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Does Vitamin D Play a Role in Depression? A Review of Clinical, Epidemiological and Biological Studies

Göran Högberg[1,2], Per Bech[3], Tore Hällström[4,5] and Maria Petersson[6]

[1]Department of Women´s and Children´s Health, Child and Adolescent Psychiatric Unit, Karolinska Institutet, Astrid Lindgren Children´s Hospital, Stockholm, Sweden; [2]Stockholm Child and Adolescent Psychiatry, BUP Huddinge, Stockholm, Sweden; [3]Psychiatric Research Unit, Mental Health Centre North Zealand, University of, Copenhagen, Denmark; [4]Department of Clinical Neuroscience, Section for Psychiatry, Huddinge, Karolinska, Institutet, Stockholm, Sweden; [5]Department of Neuroscience and Physiology, Section of Psychiatry and Neurochemistry, Unit for Neuropsychiatric Epidemiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [6]Department of Molecular Medicine and Surgery, Endocrine and Diabetes Unit, Karolinska, Institutet, Stockholm, Sweden

Abstract: There is a growing interest in the possible associations between vitamin D and depression. In this mini-review we present diagnostic criteria of different depression scales, with special focus on somatic complaints, possible links between depression and vitamin D and an overview of studies on vitamin D levels / vitamin D supplementation in depressed patients. We observed that complaints of a somatic character, potentially linked to vitamin D deficiency, are important parts of the diagnostic assessment in depression. Depressed patients often had low levels of vitamin D, and seven out of nine large (n>1000) observational studies showed an association between vitamin D levels and depression. Five studies of vitamin D supplementation in depressed patients with vitamin D deficiency showed significant reductions in depressive symptoms post-supplementation. However, only two of these studies were randomized controlled trials, and one of them had only 15 subjects. We recommend that depressed patients should generally be screened for vitamin D deficiency. Aside an increased risk of impaired bone health, individual patients may have symptoms of depression related to potentially deficient vitamin D levels. However, further randomized controlled studies of the effects of vitamin D supplementation in depressed patients are needed.

Keywords: Vitamin D, depression, observational studies, clinical trials.

INTRODUCTION

Vitamin D, activated in the skin by short-wave ultraviolet radiation, is vital for calcium balance and bone metabolism. However, vitamin D has also been suggested to have a role in various diseases such as diabetes mellitus, cardiovascular disease, multiple sclerosis, different forms of cancer and a number of mental disorders including depression [1, 2].

In the brain, cytochrome P450 enzymes convert 25OH vitamin D to active vitamin D (1,25OH vitamin D). There are vitamin D receptors (VDR) in the brain. Vitamin D seems to modulate the inflammatory system as well as influence other hormones and transmitters thought to be involved in the pathogenesis of depression. This suggests the possibility that vitamin D levels are important for mental disorders [3].

According to the Global Burden of Disease, based on disability-adjusted life years, it is predicted that depression will be the second leading cause of malady in the world by 2020 [4]. Studies in the United States have estimated the 12-month prevalence of depression to be 9% with a lifetime risk of 30% [5]. In an adolescent community sample in the United States the prevalence of depression was estimated to be between 4 and 8 percent [6]. The cumulative risk of depression has been estimated to be 29 percent for men and 45 percent for women in Sweden [7].

An association between vitamin D levels and asthenia symptoms in adults was first reported in 1979 [8]. However, research into the relationships between levels of vitamin D and symptoms of depression has been dormant until about ten years ago. More recently, an association between depressive state in elderly patients and vitamin D levels has been observed by researchers in the Netherlands [9]. Furthermore, an increase in mood and well-being has been reported following open-label vitamin D supplementation of thyroid clinic outpatients [10]. Högberg *et al.* have also showed that vitamin D supplementation in depressed adolescents increased the well-being score on the World Health Organisation (five) Well-Being Index (WHO-5) and decreased depression [11].

In this mini-review we present an analysis of the components of somatic complaints in the diagnosis of depression, associations between vitamin D and factors thought to play a

*Address correspondence to this author at the BUP Huddinge, Paradistorg 4, 141 46 Huddinge, Sweden; Tel: +46 8 514 529 00; Fax: + 46 8 514 529 05; E-mail: gorhogberg1@gmail.com

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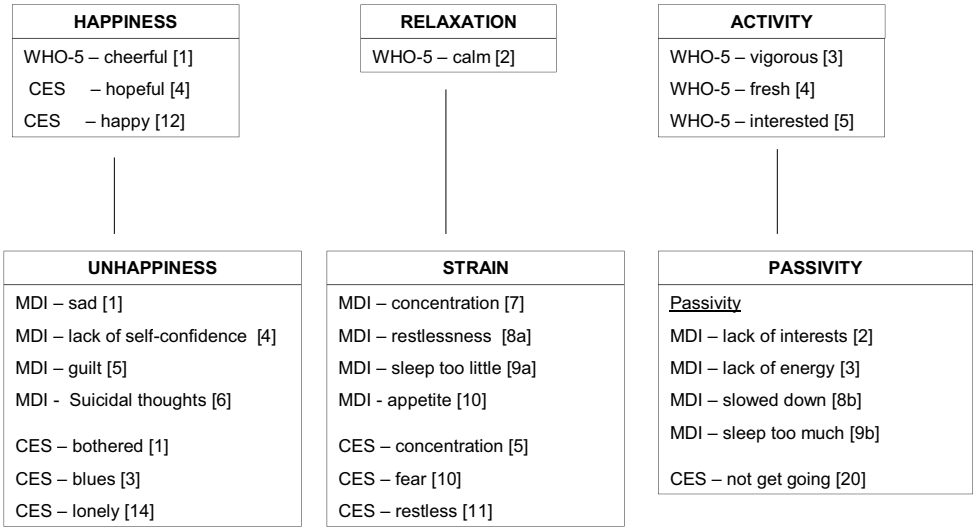

Fig. (1). Wundt´s three dimensional classification of psychological well-being versus psychological ill-being, the World Health Organisation (five) Well-Being Index (WHO-5) Center for Epidemiologic Studies Scale (CES-D), and Major Depression Inventory (MDI) items (in brackets).

role in depression, an overview of studies on vitamin D levels in depressed clinical or epidemiological samples, and an overview of vitamin D supplementation studies.

SOMATIC ELEMENTS IN THE CONCEPT OF DEPRESSION

In order to be able to discuss possible mechanisms of vitamin D in the context of depression we give a brief overview of the components of the depression diagnosis, with special focus on the somatic elements. The diagnosis of depression criteria generally includes both neurovegetative and psychological aspects, making the diagnostic umbrella large enough to encompass several clinical entities with different etiologies. This complexity concerning diagnosis can be traced back to Wilhelm Wundt (1832-1920), generally regarded as the first experimental psychologist, and responsible for establishing the first psychological laboratory in the world (1879). Wundt´s contribution to the psychometric measurement of well-being versus ill-being was his three-dimensional approach (Fig. **1**) [12], an approach that is still clinically valid [13-15]. As shown in (Fig. **1**), the WHO-5 [16] partly covers the two Wundt components of happiness and relaxation, while the component of activity is covered by the WHO-5 items of being "active and vigorous", feeling "fresh and rested", and being "interested in the daily activities".

The three components of subjective ill-being are unhappiness, strain and passivity. In (Fig. **1**), the corresponding items in the Major Depression Inventory [16] are indicated, along with the 10-item version of the Center for Epidemiologic Studies Scale (CES-D).

(Fig. **2**) shows the three clinician-administered depression scales recommended in the World Federation of Societies of Biological Psychiatry Guidelines for the treatment of patients with major depression [17]. These scales are the Hamilton Depression Scale (HAM-D) [16], the Montgomery Åsberg Depression Rating Scale (MADRS) [18] and the Bech-Rafaelsen Melancholia Scale (MES) [16]. As seen in (Fig. **2**), the Wundt component of passivity is covered by MES to a much higher degree compared with HAM-D17 or MADRS. The two other Wundt components strain and unhappiness are equally represented in the MADRS and MES whereas the physiological strain symptoms dominate in the HAM-D17.

In the scales in (Fig. **2**), the symptom of psychic anxiety is included as a core item of depression, but symptoms of psychomotor retardation have been suggested by Parker and Hadzi-Pavlovic to be the key item in depression [19]. Regarding the effects of vitamin D deficiency we would then especially expect an effect in the Wundt areas of strain and passivity, as these aspects are hypothesized to be more linked to physiology.

BIOLOGICAL LINKS BETWEEN VITAMIN D AND DEPRESSIVE SYMPTOMS

A biological link between vitamin D and mood was originally suggested by Stumpf and Privette (1989) based on findings of the effects of vitamin D in rodent brain [20]. Studies suggesting possible links between biological parameters associated with depression and vitamin D were also presented in reviews by McCann & Ames (2008) [21] and Harms *et al.* (2011) [22].

The Vitamin D Receptor

The vitamin D receptor (VDR) is a nuclear receptor which - after binding of active vitamin D, i.e. 1,25 OH-vitamin D, and interacting with co-activators - acts as a transcription factor regulating gene expression. The vitamin D-activated VDR complex can affect target genes both by activation and repression [23]. VDRs are found in almost all tissues of the body, including the gut, heart, skeletal muscle, liver, pancreas and immune system. Human lymphocytes and macrophages also have VDRs [24, 25]. In the central nervous system, a high concentration of VDRs has been demon-

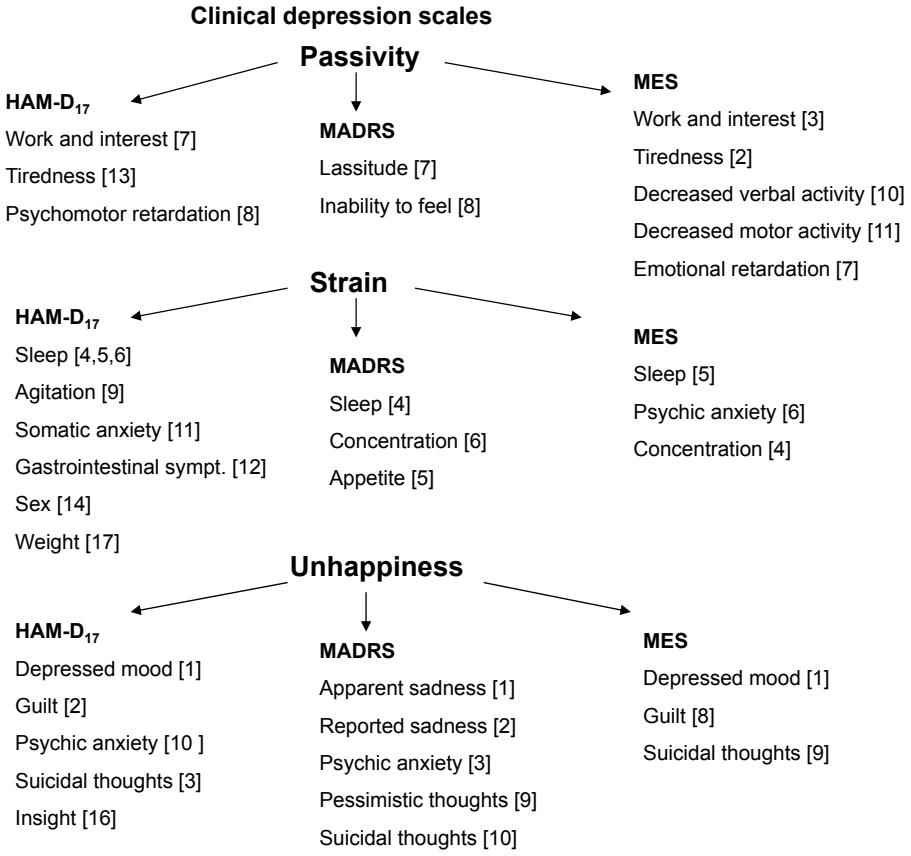

Fig. (2). Clinical depression scales related to Wundt´s three-dimensional classification, the Hamilton Depression Scale (HAM-D), the Montgomery Åsberg Depression Rating Scale (MADRS), and the Bech-Rafaelsen Melancholia Scale (MES).

strated by Eyles *et al.* (2005) [26] in the amygdala, thalamus, hypothalamus, dorsal raphe nucleus, substantia nigra, dorsal nucleus of the vagus, and in motor neurons located both in the brain, and in the spinal cord.

The effects of the VDR are modulated both by interaction with other nuclear hormone receptors and by regulation of co-activators and co-repressors. Thus a variety of factors can influence the effects of vitamin D even after binding to the VDR, some of which will be discussed later [25]. More recently, membrane bound VDRs that act more rapidly through trans-membrane signal transduction pathways have been reported [27].

Results of both animal and human studies support a role for VDRs in depression. Knockout mice which lack VDRs show more anxiety-like behavior and abnormalities in certain kinds of social behavior [28]. Burne *et al.* [29] commented that such mice showed overlapping phenomenology to animal models of depression, although there are differences in muscle strength that might explain some components of the "anxious" mice phenotype (the knockout mice showed motor impairments during swimming, but also differences in locomotor activity where at least the latter could be signs of anxiety). In addition, Kuningas *et al.* [30] have shown that variants in the VDR gene are associated with both depression and cognitive function in elderly humans. It has also been suggested that there is a special phenotype of the VDR associated with an increased risk for enhanced severity of certain diseases if these subjects become vitamin D deficient [23].

Neurogenesis and Neurotrophins

The role of cell-death and neurogenesis has been proposed to be associated with depression, and often cell-death and neurogenesis in the hippocampus are mentioned in this context [31]. There is also a neurotrophic hypothesis of depression as reviewed by Neto *et al.* [32]. A finding that further supports an association between vitamin D and depression in this aspect is that the VDR is needed for stem cell function. One hypothesized association with depression is the renewal of hippocampal cells. The hippocampus, which is part of the limbic system, contains VDRs and is involved in, among other functions, episodic memory, regulation of emotions, and the regulation of the hypothalamic pituitary adrenal (HPA)-axis [26, 33]. A correlation between vitamin D and neurotrophins, for instance nerve growth factor (NGF), has also been found [34]. These secreted proteins are of central importance for nerve cell survival and differentiation of neurons in the brain. In rodent models it was shown that vitamin D affected neuroprotection positively [35].

Motor Function

As mentioned above, there is a rich presence of VDRs in the brain, including in areas of importance for control of the endocrine-autonomic system as well as the motor system. Body weakness is a common complaint in subjects with low vitamin D, and muscular fatigue can also be a part of the somatic complaints of depressed patients. The substantia nigra, an important part of the brain for motor function, has

abundant amounts of VDRs [26] and vitamin D has been shown to increase the expression of the tyrosine hydroxylase gene [36], which is essential for the synthesis of dopamine. There is thus some mechanistic evidence for a hypothesis that stiffness and motor retardation, as encountered in some forms of depressive illness, can be related to the activity of the VDR and levels of vitamin D in the brain.

However, the effects of vitamin D on motor function are probably mostly mediated directly *via* actions on the muscle cells. There are VDRs in the skeletal muscle, and clinical studies show that vitamin D status is positively associated with muscle strength and physical performance, and inversely associated with the risk of falling [37]. A dose-response relationship between vitamin D levels and improvement in the ability to walk has also been observed [37].

The HPA-axis, other Hormones and Neurotransmitters

The stress- system aims at maintaining the physiologic homeostasis of the organism and is activated upon threats to homeostasis. The two most important factors here are the HPA-axis and the sympathetic nervous system, and VDRs are located in many areas important to the regulation of these systems. A dysregulation of the HPA-axis has been observed in patients with depression, and both higher and lower cortisol levels have been demonstrated. The lower levels of cortisol have been associated with long-lasting depression and an exhaustion of the HPA-axis. In addition, it is well-known that depressed patients, particularly those with melancholia, often show an abnormal dexamethasone suppression test [38]. It is possible that vitamin D and the VDRs are involved in these changes since the VDR gene contains a row of putative glucocorticoid responsive elements and, interestingly, cortisol has been reported to regulate VDR expression [39]. In addition, there are VDRs in both the hippocampus and the hypothalamus, which regulate activity within the HPA-axis.

Besides the VDRs in the brain, as mentioned above, vitamin D also influences the catecholamines by activating the gene expression of the enzyme tyrosine hydroxylase. This enzyme is a rate-limiting step in the synthesis of catecholamines. By this mechanism vitamin D may affect the level of the neurotransmittors dopamine, noradrenaline and adrenaline. The synthesis of acetylcholine is influenced by vitamin D as well [40].

Oxytocin and thyroid hormones are linked to stress/anti-stress, as well as behaviour and depression. Besides being a hormone, oxytocin, which is synthesized in the hypothalamus, is released within the brain where it modulates the stress response for example through effects on alpha 2-adrenoreceptors and the HPA-axis. Interestingly, a VDR binding sequence in the oxytocin receptor gene has been reported [41]. An interaction between the thyroid hormone receptor and the VDR has also been found [42].

Vitamin D has also been associated with sleep; in an uncontrolled study of 1500 subjects with sleeping disorders, supplementation produced normal sleep in most patients [43]. The hypothalamus is a key player for the diurnal rhythm, and as mentioned, the hypothalamus is richly equipped with VDRs. Nuclei in the brainstem involved with sleep are also reported as being rich in VDRs [44]. In addition, a successful resolution of hypersomnia was reported post vitamin D supplementation [45].

The Immune System

There are interactions between the stress response, especially the HPA-axis, and the immune system; inflammation activates the stress response system and vice versa [46]. The immune system and the stress system also affect the diurnal rhythm. The levels of vitamin D are thus related to the immune system by its relation to the stress response, but there are also suggestions of a direct association between the vitamin D levels and the immune system. VDRs are located in many areas of importance for immunomodulation. As mentioned earlier, human lymphocytes and macrophages have VDRs [24, 25].

There has been 20 years of "progress and discovery" concerning depressive disorders and immunity, reviewed recently by Krishnadas and Cavanagh [47], and Dantzer [48]. In several studies, depression was associated with increased immune activation and inflammation [49]. Cytokines are intercellular signalling proteins involved in regulation of inflammatory and immune responses. Recently, it has been observed that there is a shift in the balance between the pro-inflammatory and anti-inflammatory cytokines, with former increased and the latter decreased in vitamin D deficiency [50, 51]. Several agents, including cytokines, are capable of eliciting neurogenic inflammation in the brain [52, 53]. Such inflammatory responses might be associated with depressive symptoms such as general fatigue and also a feeling of sickness; "malaise" [48].

STUDIES OF VITAMIN D AND DEPRESSION

We conducted an electronic search in PubMed for articles relating to vitamin D and depression, using the search term "vitamin D" together with "depression" (n=423) or "psychiatric" (n=153). We selected English-only studies presenting original data, and excluded reviews and comments. Our searches identified 46 such studies from 1979 to 2012. Of this number, six were published between 1979 and 2005, and 40 between 2006 and 2012, mirroring the increasing interest in this area of research. In the presentations in (Tables **1** and **2**) we divided the studies according to whether they were observational studies or vitamin D supplementation studies, with three belonging to both categories.

Observational Studies

In (Table **1**), an overview of 32 studies, with both clinical and epidemiological samples, is given. Vitamin D levels in depressed patients were measured in six of these studies from Iran [54], New Zealand [55], Germany [56], Italy [57] and Sweden [11, 58]. In summary, the populations of these studies were all low in vitamin D compared with normal controls or estimated normal values in the population. Of note is that in two studies [54, 55] several subjects had very low levels (< 25 nmol/l).

Six studies examined the levels of vitamin D in relation to depressive symptoms in other diagnostic categories. These were fibromyalgia [59], cardiovascular disease [60], multiple sclerosis [61], mental disorders [62, 63], and patients receiv-

Table 1. Clinical and population-based studies (2000-2012) exploring the relation between vitamin D, wellbeing, and symptoms of depression. Effect measures: correlation (r), proportion of explained variance (R^2), hazard ratio (HR), odds ratio (OR), risk ratio (RR) and 95% confidence interval (CI). Vitamin D ng/ml mean values are transformed into mean nmol/L by a factor of 2.5.

Study, Year, Type	Population (n)	Depression/Wellbeing Measure	Statistical Method	Association Between Vit D and Depressive Symptoms, and/or Wellbeing
Schneider *et al*., 2000, cross-sectional several psychiatric diagnoses [56]	Depressed psychiatric inpatients (n=25), healthy controls (n=31)	Structured clinical diagnosis of depression (DSM-III-R)	Mann-Whitney U	Patients lower in vit D (p<0.01)
Jorde *et al*., 2006, cross-sectional [73]	Subjects with low vitamin D (n=21), normal controls (n=63)	Beck Depression Inventory (BDI)	Kruskal-Wallis	Vit D level was negatively correlated with BDI (p=0.04)
Wilkins *et al*., 2006, cross-sectional [74]	Epidemiological sample, older adults, (n=80), half with mild Alzheimer and half without dementia	Depression Symptoms Inventory	Multivariate logistic regression	Vit D deficiency positively correlated with depression (OR=11.69, CI: 2.04-66.86)
Armstrong *et al*., 2007, cross-sectional, case-series [59]	Adults with fibromyalgia (n=75)	Hospital Anxiety and Depression Score (HADS)	Kruskal-Wallis, ANOVA on ranks	Vit D level negatively correlated with HADS (p<0.05)
Berk *et al*., 2008, cross-sectional [63]	Psychiatric inpatients (n=53), community control (n=691)	Clinical evaluation	Multivariate regression	58% of patients vit D <50nmol/L. Female patients lower than controls (p<0.001)
Jorde *et al*., 2008, cross-sectional [75]	Overweight adults (n=441) divided into two subgroups	BDI	Mann-Whitney U	Group with vit D <40 nmol/L scored higher on BDI than group with higher vit D levels (p<0.05)
Hoogendijk *et al*., 2008, cross-sectional [9]	Aged people between 65 and 95 years (n=1,282)	Center for Epidemiologic Studies Depression scale (CES-D)	Multiple linear regression	Vit D level negatively correlated with CES-D score (p<0.01)
Nanri *et al*., 2009, cross-sectional [77]	Municipal employees (n=527)	CES-D	Multivariate logistic regression	No sig relationship (actual values not reported)
Pan *et al*., 2009, cross-sectional [65]	Subjects 50-70 years old. (n=3,262)	CES-D	Multivariate logistic regression	No sig relationship (actual values not reported)
Bossola *et al*., 2010, cross-sectional, case series [64]	Chronic hemodialysis patients (n=80)	BDI	Multivariate logistic regression	No sig relationship (actual values not reported)
Humble *et al*., 2010, cross-sectional chart review, several psychiatric diagnoses [58]	Depressed psychiatric out-patients (n=36), no controls	Clinical evaluation	-	Low vit D level compared to general population (actual values not reported)
May *et al*., 2010, longitudinal [60]	Adult subjects with a cardiovascular diagnosis but no previous depression (n =7,358)	Clinical diagnosis of depression at follow up	Multivariate Cox regression	Group with vit D level<43 nmol/L had higher rates of incident depression (HR=2.7, CI: 1.35-5.40, p=0.005)
Milaneschi *et al*., 2010, longitudinal [80]	Subjects ≥ 65 years (women, n=531; men, n=423)	CES-D	Generalized estimating equation model	Women Group with low vit D level had higher rates of incident depressed mood (HR=2.0, CI: 1.2-3.2, p<0.005) No sig relationship with men
Murphy PK, *et al*., 2010, case-series, longitudinal [82]	Postpartum women (n=97)	Edinburgh Postpartum Depression Scale (EPDS)	Linear mixed model	Negative correlation between vit D level and EPDS score (t=2.3, p=0.02)

Table 1. contd…

Study, Year, Type	Population (n)	Depression/Wellbeing Measure	Statistical Method	Association Between Vit D and Depressive Symptoms, and/or Wellbeing
Stewart and Hirani, 2010, cross-sectional [68]	Aged people ≥65 years (n=2,070)	The 10-item geriatric depression Scale (GDS10)	Logistic regression model	Deficiency levels of Vit D positively related to GDS10 score (OR=1.46, CI: 1.02-2.08, p=0.04) when adjusted for vitamin D supplementation and subjective health status
Zhao *et al*., 2010, cross-sectional [71]	Adults (n=3,916)	Patient Health Questionnaire-9 diagnostic algorithm (PHQ-9)	Multivariate logistic regression model	No sig relationship when adjusted for demographics, lifestyle factors and number of chronic conditions
Ganji *et al*., 2010, cross-sectional [70]	Young adults, 15-39 years old (n=7,970)	The Diagnostic Interview Schedule (DIS)	Multivariate logistic regression	Group with Vit D<50nmol/L had higher prevalence of depression than group with Vit D<75 nmol/L (OR 1.86, CI: 0.90-3.81, p=0.02)
Hoang *et al*., 2011, cross-sectional [72]	Adults (n=12,594)	CES-D	Multiple logistic regression	Negative correlation between Vit D level and depression (OR 0.92, CI: 0.87-0.97)
Kjærgaard *et al*., 2011, cross-sectional [69]	Adult non-smokers (n=8,120)	Hopkins Symptoms Checklist 10 (SCL-10)	Logistic regression analysis	Negative correlation between Vit D and depression when highest and lowest quartile of Vit D level were compared (OR 0.74, CI: 0.58-0.95)
Knippenberg *et al*., 2011, cross-sectional, case-series [61]	Patients with multiple sclerosis (n=59)	HADS	Pearson correlation coefficient	Vitamin D level negatively correlated with HADS score (r=-0.33, p=0.006)
Tolppanen *et al*., 2011, longitudinal [83]	Children were assessed with Vit D3 levels and Mood and Feelings Questionnaire (MFQ) at age 9.8 years and only MFQ at age 13.8 years (n=2,130)	Mood and feelings questionnaire (MFQ)	Logistic regression	Negative correlation between Vit D and depression (RR 0.90, CI: 0.86-0.95)
Cassidy-Bushrow *et al*., 2012, cross-sectional [81]	Pregnant second trimester women (n=178)	CES-D	Logistic regression	Negative correlation between Vit D level and depression (OR 0.54, CI: 0.29-0.99, p=0.046)
Brandenbarg *et al*., 2012,cross-sectional [67]	Pregnant women (n=4,389)	CES-D	Logistic regression	The groups of Vit D deficiency or in-sufficiency had increased prevalence of depression compared to group with normal values (OR 1.48, CI: 1.13-1.95, and OR 1.44, CI: 1.12-1.85 respectively)
Brouwer-Brolsma *et al*., 2012, cross-sectional [78]	Elderly subjects (n=118)	Geriatric Depression Scale (GDS)	Multiple Poisson regression	No sig relationship (actual values not reported)
Cizza G *et al*., cross-sectional, 2012 [57]	Premenopausal depressed women depression (n=89), controls (n=44)	Diagnostic and Statistical Manual (DSM-IV) criteria, the Hamilton Depression Scale (HAM-D)	t-test and non-parametric test	The depressed group had lower Vit D level (p<0.05)
Jaddou *et al*., 2012,crossectional [66]	Adults (n=4,002)	The Depression Scale of the Depression Anxiety Stress Scales (DASS21)	Multiple logistic regression	Lowest quartile of Vit D level had higher prevalence of depression than highest quartile (OR=1.48, p=0.00)
Leedahl *et al*., cross-sectional, retrospective chart review, 2012 [62]	Psychiatric inpatients (n=548)	Patient Health Questionnaire (PHQ-9)	ANOVA	No sig relationship

Table 1. contd…

Study, Year, Type	Population (n)	Depression/Wellbeing Measure	Statistical Method	Association Between Vit D and Depressive Symptoms, and/or Wellbeing
Högberg *et al.*, 2012, cross-sectional, case-series [11]	Depressed adolescents (n=54)	The WHO-5 Wellbeing Scale	Spearman rank correlation test	Negative correlation between Vit D level and wellbeing (r=0.42, p<0.05)
Jamilian *et al.*, 2012 cross-sectional, [54]	Patients with depression (n=100), and normal controls (n=100)	(DSM-IV) criteria	ANOVA, post-hoc analysis of Tukey	Group with depression had lower Vit D level (p<0.001)
Kjærgaard *et al.*, 2012, nested case-control study, cross-sectional [76]	Subjects with Vit D level <55 nmol/L (n=230) compared with subjects with Vit D level >70 nmol/L (n=114)	Montgomery Åsberg Depression Rating Scale (MADRS)	Mann-Whitney U	Group with low Vit D levels had higher MADRS score (p<0.05)
Kwasky & Groh 2012,cross-sectional, [79]	College students (n=139)	BDI-II	t- test, Pearson correlation	No sig relationship (actual values not reported)
Menkes *et al.*, 2012, cross-sectional case-series several psychiatric diagnoses [55]	Psychiatric inpatients with depression (n=17)	DSM-IV	t-test	Median Vit D value (48 nmol/L) was considerably less than for healthy population

Table 2. Studies of Vitamin D supplementation in subjects with or without symptoms of depression 1979-2012. The mean values of Vitamin D have been transformed from ng/ml to nmol/L by a factor of 2.5.

Study, Year	Study Design, Subjects (n)	Mean Vitamin D Levels at Baseline and post supplementation	Measure of Depression	Supplementation with Vitamin D	Association Between Vitamin D Supplementation and Mental status
Bech and Hey, 1979 [8]	Case series, 43 adults after intestinal bypass surgery, divided into asthenic and non-asthenic groups	Asthenic group: 18 & 24 nmol/L Non asthenic group: 19 & 64 nmol/l.	BDI, 35 items	Initially 1,600 IU vitamin D_3 daily, then interrupted supplementation during six weeks, then same supplementation repeated	The asthenic group did not show an increase their Vitamin D levels, indicating uptake difficulties. This suggests an association between asthenia and Vitamin D deficiency, as the lack of uptake probably existed before the study.
Harris & Dawson-Hughes, 1992 [85]	RCT. Women aged 43 to 72 (n=250), 1 year study, all received calcium, half also had Vitamin D	Not reported	The Profile of Mood States (POMS)	400 IU plus calcium daily, controls had only calcium	No sig difference between the groups (non-parametric statistics); actual values not reported
Lansdowne and Provost, 1998, [84]	RCT. Adults (n=44)	Not reported	Negative affect from the Positive and Negative Affects Schedule (PANAS)	400 IU or 800 IU vitamin D_3 for five days, controls Vitamin A	Improvement in the positive affect items, (ANOVA, p<0.001)
Gloth *et al.*, 1999 [91]	RCT. Subjects with seasonal affective disorder (n=15)	28 nmol/L increased by 74% in the supplementation group and by 36% in the phototherapy group	Hamilton Depression Rating Scale (HDRS), scales for seasonal affective disorder (SAD-8)	100,000 IU ergocalciferol single dose. Controls had phototherapy	Improvement in the HDRS and SAD-8 scores in the supplementation group (regression analysis p<0.05)
Vieth *et al.*, 2004 [10]	RCT. Thyroid clinic outpatients (n=82)	About 50 nmol/L before, and about 100 nmol/L after	A wellbeing scale based on depression-screening tools and including questions on energy and mood	4,000 IU Vit D_3 daily in one group and 600 IU daily in the other group for at least 3months	The wellbeing score improved more in the high dose group than in the low dose group (Mann-Whitney, p=0.04)

Table 2. contd…

Study, Year	Study Design, Subjects (n)	Mean Vitamin D Levels at Baseline and post supplementation	Measure of Depression	Supplementation with Vitamin D	Association Between Vitamin D Supplementation and Mental Status
Dumville *et al*., 2006 [86]	RCT. Women ≥70 years old (n=2,117)	Not reported	Mental component score, calculated from the SF-12 questionnaire (MCS)	800 IU Vit D plus calcium daily for six months, no supplementation in controls	No sig difference between the groups regarding MCS score (p=0.262)
Jorde *et al*., 2008 [75]	RCT. Overweight adults (n=334)	Group was divided at baseline into two sub-groups, higher or lower than 40 nmol/L. Levels of vitamin D pre- post were 55-112, and 52-88 nmol/L respectively	BDI	20,000 IU or 40,000 IU Vit D_3 weekly for 1 year, controls were placebo	There was a significant improvement in BDI score in vit D group compared with placebo (Wilcoxon-signed ranks test $p<0.01$)
Arvold *et al*., 2009 [90]	RCT. Adult primary care patients (n=68)	Baseline 25-63 nmol/L. The increase after supplementation was 68 nmol/L	Fibromyalgia Impact Questionnaire (FIQ)	50,000 IU Vit D_3 weekly for 8 weeks, placebo con-trols	Sig improvement in FIQ (t-test, $p<0.05$)
Shipowick *et al*., 2009 [94]	Case-series. Adult women (n=6)	55 nmol/L, post supplementation 120 nmol/L	BDI-II	5,000 IU Vit D_3 daily during two months	Improvement in BDI-II score (t-test, p=0.02)
Dean *et al*., 2011 [87]	RCT. Young adults (n=128)	76 nmol/L, only ten subjects had baseline concentration lower than 50 nmol/L, after supplementation 98 nmol/L	BDI	5,000 IU daily for six weeks, placebo-controls	No sig difference between the groups (p=0.12)
Zanetidou *et al*., 2011 [96]	Elderly outpatients with depression and taking an antidepressant (n=39); open comparison be-tween treated (n=24) and controls (n=15)	At baseline treated cases had 50% mild deficiency (40-75 nmol/L) (n=22), and in the controls the vit D level was<40 nmol/L (n=10)	HDRS	Single dose 30,0000 IU Vit D_3, controls no treatment	Sig decrease in HDRS score in treatment group (t-test, p=0.02)
Sanders *et al*., 2011, [88]	RCT, community sam-ple. Women ≥ 70 years with an identified risk for hip fracture (n=2,317)	Not reported for the entire population	The General Health Questionnaire (GHQ-12), the WHO Well-being Index	50,0000 IU Vit D_3 once a year over 3-5 consecutive years, or placebo treatment	No sig difference between the groups (p=0.5)
Bertone & Johnson *et al*., 2012 [89]	RCT. Postmenopausal women (n=2,263)	Not reported	Burnam 8-item scale for depressive disorders	400 IU plus 1,000 mg calcium daily for two years, placebo controls	No sig difference between the groups; Burham score ≥0.06 of 1.16 (95% CI: 0.86, 1.56)
Högberg *et al*., 2012 [11]	Case-series, adolescents with clinical depression (n=48)	41 nmol/L before and 92 nmol/L after	WHO-5 wellbeing scale (WHO-5), Mood and feelings Questionnaire, short version (MFQ-S), a Vitamin D Deficiency Scale (VDDS)	4,000 IU daily for one month, then 2000 IU daily for two months	Improved scores in WHO-5, MFQ-S and VDDS (Wilcoxon-signed ranks test, $p<0.05$)
Khoraminya *et al*., 2012 [97]	RCT. Adults with clinical depression (n=42)	59 nmol/L before, after supplementation 118 nmol/L	BDI, HDRS	1,500 IU Vit D_3 daily plus fluoxetine, controls only fluoxetine	Improved HDRS and BDI scores (ANOVA, p=0.006 and p=0.013 respectively)

Table 2. contd…

Study, Year	Study Design, Subjects (n)	Mean Vitamin D Levels at Baseline and post supplementation	Measure of Depression	Supplementation with Vitamin D	Association Between Vitamin D Supplementation and Mental Status
Kjærgaard *et al.*, 2012 [76]	RCT. Adults from a community sample with low Vit D (n=230)	47 nmol/L before and 148 after supplementation	BDI, The Hospital anxiety and Depression Scale (HADS), The Seasonal Pattern Assessment Scale (SPAQ), Montgomery-Åsberg Depression Rating Scale (MADRS)	20,000 IU Vit D_3 weekly, placebo controls	No sig difference between the groups; p=0.929
Yalamanchili & Gallagher, 2012 [95]	RCT. Elderly community-dwelling women (n=488) divided into hormone therapy (estrogen), Vitamin D, Vitamin D + hormone, and placebo groups	78 nmol/L pre-supplementation, post-supplementation value not reported	Geriatric Depression Scale (GDS)	Calcitriol 0.25 g BID	The patients in the subgroup with depression (n=57) improved irrespective of treatment

ing hemodialysis [64]. The study by May *et al.* [60] on subjects with cardiovascular disease in the US had a large sample size, with 7,350 participants. In this study 64 percent of participants were low in vitamin D levels, with 18 percent being so low as to risk impaired bone health. In patients with multiple sclerosis and fibromyalgia (but not in hemodialysis patients) the levels of vitamin D were associated with symptoms of depression. Both studies with mental disorders showed low levels of vitamin D, but in the large (n=548) study by Leedahl *et al.* [62] there was no association between hypovitaminosis D and depressive symptoms.

There were nine large (n >1,000) cross-sectional studies on normal populations (China [65], Jordania [66], Holland [9, 67], England [68], Norway [69] and the US [70-72]). In all but two [65, 71] an association was found between vitamin D levels and symptoms of depression. In seven smaller cross-sectional epidemiological studies with sample sizes ranging from about 20 to 500, four reported an association between levels of vitamin D and symptoms of depression [73-76], while three reported no such association [77-79]. Finally, there were five longitudinal studies; from Italy with older adults (n=954) [80], from the US with prepartum (n=178) as well as postpartum women (n=97) [81, 82], and with cardiovascular patients (n=7,350) [60], and from Finland with children (n=2,752) [83]. All five studies showed a relation between low levels of vitamin D and the development of symptoms of depression.

Despite of the strength of the observations of a relation between levels of vitamin D and depression it cannot be concluded that there is a causative link between low vitamin D and depression as the converse might also be true; that depressed individuals live a life with diminished intake and production of vitamin D.

Supplementation Studies with Non-depressed Subjects

Eleven randomized controlled studies (RCTs) included subjects without any diagnosis of depression. Of these studies vitamin D supplementation had a preventative effect on subsequent development of depression in three [10, 75, 84], the latter two of which reported low levels of vitamin D for study participants at baseline. In six studies there was no such effect [76, 85-89], and two of these studies reported initial low levels of vitamin D.

In an RCT with primary care patients with different symptoms [90], a fibromyalgia impact questionnaire (FIQ) was used as an outcome variable; the authors chose this scale as it captured many of symptoms they had noticed in vitamin D deficient patients such as aching muscles, bones, joints and fatigue. This sample hade moderately low levels of vitamin D. After supplementation there were significant positive changes in five of the 20 items of the FIQ, namely ability to walk several blocks, drive a car, climb stairs, tiredness, and stiffness.

An early supplementation study by Bech and Hey [8] investigated 43 obese patients who had undergone intestinal bypass surgery and who had received 1200 IU vitamin D orally per day over a year postoperatively. This study used an expanded Beck Depression Inventory (BDI) with 35 items, including neurovegetative symptoms. At the first assessment of these postoperative patients they had stopped the vitamin D therapy six weeks previously. The next time the patients were assessed was 6 months later, and during this 6-month period they had again received 1200 IU vitamin D daily. When analyzing the 35 BDI items individually, the 12 items with the highest scores were self-dislike, irritability, work retardation, insomnia, fatigability, tiredness, aches and pains, loss of libido, headache, vertigo, palpitations, dryness of the mouth, and thirst. This 12-item subscale was termed the asthenia scale. The patients who were not able to normalize the concentrations of vitamin D after supplementation had high asthenia scores, which led the authors to conclude that: "…the asthenic symptoms reported seemed to be caused by disturbances in the vitamin D complex".

Supplementation Studies with Depressed Subjects

The first study on depressed adult patients (seasonal affective disorder) - with low levels of vitamin D who were supplemented with vitamin D in a RCT was done by Gloth *et al.* [91]. They compared eight subjects who received 100,000 IE vitamin D in a single dose with seven subjects receiving full-spectrum photo-therapy. This study used ergocalciferol, and it has been debated whether ergocalciferol is as efficient for increasing vitamin D levels as cholecalciferol, but based on previous studies it is difficult to make a firm conclusion [92, 93]. Increase in vitamin D levels was observed in both groups, but the increase was greater in the supplemented group. When both groups were analyzed together there was a significant relation between change in vitamin D level and seasonal affective disorder scores (SAD-8). When assessed at four weeks, there was a significant lowering of the scores on the Hamilton Depression Rating Scale (HDRS) and on SAD-8 of the subjects who received vitamin D supplementation, but not the phototherapy group.

In a supplementation study on depressed adolescents by Högberg *et al.* [11], 48 depressed adolescents (35 of whom had severe depression with suicidality or self-harm behaviour) had an average initial vitamin D level of 41 nmol/L (measured as 25 OH vitamin D). The vitamin D level reached 92 nmol/L after three months of supplementation, consisting of 4000 IU daily the first month and 2000 IU daily the following two months. Post supplementation there was a significant improvement on the WHO-5 and on the depression rating scale Mood and Feelings Questionnaire short version (MFQ-S). The results also showed a significant improvement in the following items from a vitamin D deficiency/depression scale: tired during the day, insomnia, body weakness, aches and pains, depressed feeling, irritability, difficulties with mood regulation, and difficulties with concentration.

In a study by Shipowick *et al.* [94] six women who were initially low in vitamin D (mean <55 nmol/L) initiated supplementation with 5000 IE vitamin D3 daily for eight weeks. The average increase in levels of vitamin D was 68 nmol/L. Pre- and post-supplementation the Beck Depression Inventory (BDI) was completed, with a decrease from a mean score of 32 initially (severe depression) to a mean score of 22 (moderate depression) observed. Three of the women reached a post-supplementation level of vitamin D of 120 nmol/L and these subjects had BDI-scores of 14 or below (normal mood).

Yalamanchili and Gallagher (2012) presented the results of a study with 57 depressed postmenopausal women with normal vitamin D levels [95]. These women were randomized to hormone therapy, placebo treatment, hormone therapy with calcitriol, and calcitriol only.

All the four treatment arms showed a significant improvement in depression. It is of note that in this study the active metabolite of vitamin D, calcitriol (1.25 dihydroxycholecalciferol), was used, which makes comparisons with other studies with oral vitamin D3 hard to evaluate.

Zanetiodu *et al.* [96] conducted an open case-control study of depressed women aged >65, who were taking antidepressants. Twenty-four cases were administered a single oral dose 300 000 IE vitamin D. Depressive symptoms were rated with the HDRS at baseline and after 4 weeks. Fifteen subjects were administered usual care as comparator. Before supplementation both groups had a HDRS score of 21, but after 4 weeks the HDRS scores were significantly lower in the treated group. Both groups were low in vitamin D but there was no information on vitamin D levels post-supplementation.

In the RCT by Khoraminya *et al.* [97] 40 adult subjects with a diagnosis of depression completed an eight week study. The vitamin D level at baseline was 58nmol/L, which was moderately low. The sample was divided into two groups; one receiving the antidepressant fluoxetine plus 1500 IE vitamin D3 daily and the other receiveing fluoxetine plus placebo in a double-blind placebo-controlled design. At baseline, there was a negative correlation between depression scores and vitamin D levels. After about four weeks a significant decrease in the depression scores on HDRS and BDI was observed in the fluoxetine plus vitamin D group, but such result was not observed in the fluoxetine only group.

CONCLUSION

Low levels of vitamin D are present in patients diagnosed with depression, with a proportion of very low levels with risk for impaired bone health. Accordingly we suggest that depressed patients be considered a risk group for osteomalacia. Some positive results have been observed in studies involving the use of vitamin D supplementation for management of depression, but the number of RCTs is too few to draw any conclusions. There is thus a need for further such randomized controlled trials. We offer in the appendix a proposal for a depression and vitamin D deficiency index (Hogberg index of depression and vitamin D deficiency) aimed at finding linked variables based in part on the studies of Bech *et al.* [8] and Högberg *et al.* [11]. This Index, which is not a validated scale, relates strongly to the aspects of "strain" and "passivity" in the original Wundt diagnostic system [12]. We recommend that in future studies, subjects who are diagnosed with a validated scale as clinically depressed, and showing evidence of vitamin D deficiency, be given dosages of vitamin D large enough to normalise serum levels.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

APPENDIX

Hogberg Index of Depression and vitamin D Deficiency

Please do show on the line how true you experience the statement regarding the last **two weeks**. The number ten means that you experience the statement as very valid and the number zero that it is not at all true.

I have been tired

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have been physically weak

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had aches and pains

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

My sleep has been poor

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have felt depressed

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have felt irritated

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had mood swings

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had difficulties in concentrating

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had less interest in sex than usually

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

My mouth has felt dry

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had headache

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had vertigo

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have had palpitations

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have been disliking myself

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

I have been stiff in my body

0…...1…...2…..3…..4…..5…...6…..7…...8…...9……10

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