Vitamin D Deficiency and Suicide

Miriam Salamon
Miriam Salamon will graduate with a BS in Biology in June 2017.

Abstract
Vitamin D deficiency, in an increasingly modernized world, is a major global health issue and so is major depressive disorder (MDD) and its high fatality risk. Studies suggest that there may be a connection between the two. Several studies have found a connection between low levels of vitamin D and higher rates of major depressive disorder, depressive symptoms and suicidal ideation. Specifically, lower concentrations of vitamin D was seen in the subgroup of patients with suicidal thoughts when comparing with non-suicidal depressed patients. A likely reason for this may be the well- researched role vitamin D plays in regulation of inflammatory cytokine markers in the brain. Elevation of these proinflammatory cytokines is shown to be a major contributing factor to depression and suicidality. Therefore, a lack of vitamin D contributes to an increase in inflammation and thereby an increase in the risk of depression and suicide. Thus, increasing vitamin D levels by supplementation or sun exposure, may decrease depressive symptoms. Because this research is recent, there are few studies assessing the possible benefits and limitations of using vitamin D as a treatment method.

Introduction
Vitamin D_3 is a fat soluble vitamin, stored mainly in the liver and adipose tissue. It is primarily obtained by the conversion of cutaneous 7-dehydrocholesterol to previtamin D_3 by sunlight, specifically Ultraviolet (UV) B radiation with a wavelength of 290–320 nanometers. Previtamin D_3 then spontaneously isomerizes to vitamin D_3, or cholecalciferol. Vitamin D3 is biologically inert and must undergo two hydroxylation to be biologically active. The first hydroxylation occurs in the liver, by 25-hydroxylase, converting vitamin D3 to calcidiol, or 25-hydroxyvitamin D [25(OH)D]. The second hydroxylation occurs by 1α-hydroxylase, found primarily in the kidneys, although recent research found this enzyme in many other tissues. The second hydroxylation converts the 25-hydroxyvitamin D to the biologically-useful calcitriol, or 1,25-dihydroxyvitamin D [1,25(OH)2D] (Vitamin D: Fact, 2016).

Besides for obtaining vitamin D by sun exposure, vitamin D can be obtained by food. However, very few foods in nature contain vitamin D. Therefore, a better way of obtaining vitamin D is from cholecalciferol-fortified foods or supplements (Vitamin D: Fact, 2016).

Serum concentration of 25-hydroxyvitamin D is the best indicator of vitamin D status, because it reflects vitamin D obtained by sun exposure and ingestion. It also has a fairly long circulating half-life of 15 days and its concentration is not affected by other metabolites. However, it does not indicate how much vitamin D is stored in body tissues. In contrast, 1,25-dihydroxyvitamin D has a short circulating half-life of 15 hours and its levels are closely regulated its own concentration and by hormones and electrolytes like parathyroid hormone, calcium, and phosphate. Additionally, levels of 1,25(OH)2D only decreases when vitamin D deficiency is severe. Therefore, 25-hydroxyvitamin D levels are used to assess sufficiency (Vitamin D: Fact, 2016).

There is considerable discussion of what serum concentrations of 25-hydroxyvitamin D indicate vitamin D deficiency, adequacy for bone health and optimal health overall. As of now, there is no specific cut points established by a scientific consensus process. However, the committee of the Institute of Medicine, based on its review of data of vitamin D needs, have concluded that there is a risk of vitamin D deficiency at serum 25(OH) D levels of less than 30 nmol/L (<12 ng/mL). Additionally, some people are potentially at risk for inadequacy at concentrations ranging from 30-50 nmol/L (12–20 ng/mL). They stated that 50 nmol/L is the serum 25-hydroxyvitamin D level that is adequate for 97.5% of the population. Only at concentrations of greater than 125 nmol/L (>50 ng/mL) is there potential adverse effects of overdose (Vitamin D: Fact, 2016).

Cutaneous vitamin D levels are mainly dependent on climate, overall skin exposure, skin melanin content and age. Residing in a climate closer to the equator results in more year-round sun exposure and more vitamin D synthesis. Although surprisingly, geographic location does not consistently predict average serum levels in a population. Opportunities exist to form vitamin D from exposure to sunlight during the spring, summer, and fall months even in the far north or south, and it can be stored in fat for periods of little sunlight. Darker skin absorbs less sunlight and, therefore, more melanin reduces the production of vitamin D. Perhaps, this characteristic may contribute to the consistency in average serum levels of those near the equator and those further away, because those who live near the equator generally have a darker skin tone that synthesis less vitamin D than those farther away with a lighter skin tone. Vitamin D synthesis may also decline with age because skin synthesis declines (Johnson, 2016).

Major depressive disorder (MDD) is a common disorder and leading source of disability worldwide. It is a major global health problem, with more than 50% of all suicides contributed to clinical depression (Bay-Richter, Janelidze, Hallberg, & Brundin, 2011). Classically, the prevailing hypothesis on the cause of major depression was a deficiency of monoamines, a class of neurotransmitters and neuromodulators, like serotonin. Therefore, current available medications for major depression mainly target monoamine pathways. However, research has not shown a consistent relationship between serotonin and depression

(Gardner & Boles, 2011). And although relatively affective, 30% of depressed patients do not achieve remission even with multiple, monoamine-regulating, treatment trials (Miller, Maletic, & Raison, 2009). Additionally, 50% to 80% of all patients treated for major depression will experience relapse (Bay-Richter, Janelidze, Hallberg, & Brundin, 2011). These monoamine regulating drugs can have serious side effects, which include worsening of depressive symptoms and suicidal ideation. Therefore, it is imperative to find novel pathways involved in depression and consequently more effective treatments for those suffering.

Historically, in literature, and in art and religion, happiness and positivity have been associated with summertime, daylight, and sunny and open landscapes. In contrast, fear and gloom have been associated with winter, night and dark and polluted urbanscapes. At the height of early industrialism, in such polluted cities, rickets, which is extreme vitamin D deficiency was first recognized. Among the symptoms of rickets, mental symptoms were also described and Florence Nightingale stated: "People say the effect [of sunlight] is on the mind. So it is, but the enlightened physician tells us it is on the body too." (Humble, 2010) Mental disturbances caused by reduced sun exposure seemed self-evident that no one seemed to note the mental health benefits of rickets treatment, which was primarily to increase sun exposure. Because of the awareness of adequate sun exposure, rickets disappeared as a public health problem. Nevertheless, from the 1950s and on, with increasing modernization, the time spent indoors increased for all ages worldwide. Additionally, since the 1980s, the public is being warned about the dangers of UV rays and its contribution to malignant melanoma. Therefore, people have developed concern of excessive sun exposure and are applying sunscreen and covering up more when they are outside. At the same time, as these changes are taking place, the incidence of depression, especially in children and adolescents, has become more and more prevalent in the United State and Europe (Humble, 2010). Additionally, it is a long, well-known and perplexing observation that death by suicide is highest in the springtime for people living in temperate climates, which is also when vitamin D levels are the lowest in the population (Umhau et al., 2013). Is there a correlation between these two observed phenomena of depression and vitamin D synthesis, and what would be there relationship?

Materials and Methods

Materials for this comprehensive review were obtained from Touro College's online library, PubMed, PubMed central, Proquest, National Institute of Health website and Merck Manual website. The material consisted of clinical research papers, peer-reviewed journal articles and clinician-directed informational reports. The material was reviewed, critically analyzed and compiled to answer research questions.

Discussion

Vitamin D and Inflammation:

Classically, Vitamin D is associated with bone health. Vitamin D aids calcium absorption in the gut and maintains adequate serum calcium and phosphate levels for normal mineralization of bone (Vitamin D: Fact, 2016). It is also needed by osteoblasts and osteoclasts bone growth and repair. Vitamin D deficiency was mostly associated with rickets and osteomalacia at extreme deficiency. Rickets is a disease in children where vitamin D deficiency leads to bones not being able to properly mineralize, which results in soft bones and skeletal deformities. In adults, vitamin D deficiency can lead to osteomalacia, or weak bones (Vitamin D: Fact, 2016).

Recently, many other functions of vitamin D have been discovered and vitamin D receptors have been found in many tissues. One of the most significant findings is the function of vitamin D in immune system modulation. There is an increasing number of studies that demonstrate the importance of vitamin D in the reduction of inflammation and the association of vitamin D deficiency with increased inflammation (Peterson & Heffernan, 2008). Most of the known effects of vitamin D are facilitated through vitamin D receptors (VDR). These vitamin D receptors have been found extensively in immune system cells, specifically in T lymphocytes and macrophages. Furthermore, macrophages have been found to express 1α-hydroxylase, which is the enzyme that is responsible for the final step in synthesizing biologically-active vitamin D. Additionally, they have been found to express 24-hydroxylase, the major degrading enzyme of vitamin D. This means that these cells can regulate the production and secretion of vitamin D in their own vicinity (Peterson & Heffernan, 2008).

Additional evidence now suggests that vitamin D insufficiency may play a role in immune system dysfunction and low 25-hydroxyvitamin D serum levels are shown to be associated with autoimmune diseases like multiple sclerosis, Type 1 diabetes and rheumatoid arthritis. Recently, this insufficiency has been correlated to macrophage dysfunction, such as impaired chemotaxis, phagocytosis and increased production of proinflammatory cytokines. Proinflammatory cytokines are produced predominantly by activated macrophages. These cytokines take part in cell signaling and up-regulation of inflammatory reactions. Vitamin D has been shown to reduce inflammation by down-regulating the expression of monocyte toll-like receptors (TLRs), which are known to activate inflammation and aggravate autoimmune disease and sepsis (Peterson & Heffernan, 2008).

In light of the research, Peterson and Heffernan (2008) sought to investigate the relationship between serum vitamin D status (25(OH)D) and inflammatory markers in 69 healthy women.

They recruited people with high UVB and minimal UVB exposure, as assessed by a screening questionnaire, to obtain a range of serum levels. Volunteers were excluded for multiple factors, including, if they took a vitamin D supplement, had a current or previous medical condition or took medication affected immune function. The results revealed that serum TNF-α, a proinflammatory cytokine, was significantly lower in the group of women with high UVB exposure, after controlling for multiple factors. However, there was no significant statistical difference shown between the two groups in regards to other proinflammatory cytokines, like IL-10, CRP, IL-6. Serum TNF-α concentrations are increased in several diseases like multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, heart disease and osteoporosis, and lowering TNF-α concentrations through sufficient vitamin D levels may improve disease outcomes. The main limitation of this study was the small sample size. Additionally, women who frequently tan are characteristically different from non-tanners and may engage in behaviors that can affect the study outcomes. This study shows a negative correlation between vitamin D status and TNF-α concentration in healthy individuals. More research is needed to determine if vitamin D can be used as a therapy in inflammatory diseases.

A case where vitamin D deficiency seems to contribute to immune modulation, is in diabetic foot infection. Diabetic foot infection is a reflection of a diabetic patient's altered immune system. In an infectious state, pro-inflammatory cytokines are released in the body, such as IL-1β, IL-6, interferon-γ (IFN-γ) and TNF-α, or chemokines such as IL-8. To counteract these factors and avoid a hyper-inflammatory state, the body releases anti-inflammatory cytokines such as IL-10. In a diabetic patient, several factors lead to decreased wound-healing abilities, including impaired cytokine production. This abnormal wound healing is attributed to immune dysregulation because of vitamin D deficiency in addition to hyperglycemia (Timms et al., 2002).

Another study, investigating the relationship between vitamin D deficiency and increased inflammatory cytokines, was done by Timms et al. (2002), by evaluating the influence of vitamin D on the concentrations of IL-1β, TNF-α, IFN-γ and IL-6 in patients with diabetic foot infection. Subjects were 112 diabetic patients with diabetic foot infection while 107 diabetic patients with no evidence of infection served as controls, additionally, 40 healthy subjects were included in the study. Vitamin D deficiency, a serum 25-hydroxyvitamin D < 50 nmol/l, was found in 71.4% of the diabetic foot infection patients, 61.6% of the diabetic controls and 48.6% of the healthy volunteers, but severe deficiency, with a serum 25-hydroxyvitamin D of < 25 nmol/L, was mostly found in diabetic foot infection patients than in diabetic controls and healthy volunteers. In both patients and controls, 25-hydroxyvitamin D levels was found to be significantly negatively correlated with IL-1β as well as IL-6 levels and moderately negatively correlated with TNF-α levels, but not correlated with IFN-γ levels. In this study, diabetic patients with foot infection serve as a model for immune system abnormality resulting from hyperglycemia and infection, with increased pro-inflammatory cytokine concentrations. The results of the present study showed that elevated cytokine responses occur as a factor of vitamin D deficiency in patients with diabetic foot infection. Vitamin D deficiency, particularly when serum levels were very low, intensified inflammatory cytokine release in patients with diabetic foot infection.

Because of this increasingly strong correlation and possibly causation of vitamin D deficiency to amplified inflammation, and to try to prove causation more visibly, Hoe et al. (2016) recently performed a study ex vivo. They studied the effects of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D, on peripheral blood mononuclear cells (PBMCs) and purified immune cell subsets isolated from healthy patients, when they exposed those cells to stimulation with Gram-positive heat-killed pneumococcal serotype 19F (HK19F) and Gram-negative Escherichia Coli serotype 055:B5 derived lipopolysaccharide (LPS) bacterial ligands. They found that in 1,25(OH)2D3 pretreated samples compared to non-treated, for both ligands, 1,25(OH)2D3 suppressed proinflammatory cytokines, like TNF-α, IFN-γ and IL-1β, and chemokine IL-8, in peripheral blood mononuclear cells (PBMCs) and TNF-α and IL-1β in CD14+ Monocytes. Anti-inflammatory IL-10 was increased in HK19F-stimulated monocytes. Additionally, when comparing the blood samples of the healthy subjects, they found that levels of HK19F-specific IFN-γ were significantly higher in vitamin D-insufficient adults (<50 nmol/L) compared to sufficient adults (>50 nmol/L). This study suggests Vitamin D causes modulation of inflammation of the immune system response which is critical for host defense.

Inflammation and Depression

The progression and complications of many diseases and disorders, like cardiovascular disease, diabetes and cancer, are being increasingly attributed to inflammatory dysfunction. Additionally, this theory of disorder is being extended to neuropsychiatric disorders, with mounting evidence suggesting that defective alterations of the immune system seen in psychiatric patients may contribute to their disorders, and with mounting evidence of inflammation contributing to major depressive disorder. Patients with major depression have been found to exhibit elevated proinflammatory cytokines, like IL-1β, TNF-α and IL-6, which have been shown to interact with areas known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Furthermore, psychosocial stress, a common precipitator to major depression, has been shown to have the ability to stimulate inflammation, owing to

the fact that it activates sympathetic nervous system pathways. Moreover, depressed patients with increased inflammatory markers have been found to have greater resistance to treatments, and in studies, antidepressant drugs have been found to be correlated with decreased inflammation (Miller, Maletic, & Raison, 2009).

Recurrent coinciding comorbidities and drug efficacies suggest that depression is part of a group of related conditions, all of which are associated with inflammation dysfunction. They are sometimes referred to as the "affective spectrum disorders", and include migraine, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and generalized anxiety disorder, among many others. Based on current knowledge, these diseases, including depression, seem to be a function of three connected abnormalities: monoamine dysfunction, increased inflammation, and mitochondrial disorder (Gardner & Boles, 2011)

To test if inflammation may correlate or even cause major depression, several studies performed on animals who have been injected with the endotoxin lipopolysaccharide (LPS) to generate inflammation, showed that these subjects subsequently developed depressive-like symptoms. In clinical practice, it has been seen that patients treated with interferons and interleukins, to promote inflammation against certain forms of cancer and viral infections, like Hepatitis C, frequently develop depression. To further investigate this relationship Bay-Richter, Janelidze, Hallberg, & Brundin (2011) induced inflammation in rats by administering Escherichia coli serotype 055:B5 lipopolysaccharides (LPS) intraperitoneally for four days. They measured their levels of cytokine markers at the state of sickness and then at the state of depressive-like behaviors. They also measured mRNA transcription of cytokines in specific brain areas related to depression as well as levels of cytokines in serum and cerebral spinal fluid. Cyclooxygenase enzymes, inflammatory stimulating COX-1 and COX-2, have previously been shown to correlate with depressive-like behavior, thus, it is suggested that proinflammatory cytokines can induce depressive-like behavior by activating prostaglandins, and inflammation, through the cyclooxygenase enzyme. Therefore, they also measured cyclooxygenase enzymes in the brain of the mice. This is the first published study examining the relationship between proinflammatory cytokines and cyclooxygenase enzymes in the blood, CSF and depression-related brain areas and their capacity to cause sickness and behavioral changes.

In this study, they found that there was a clear distinction between the phase of sickness, which is 2 hours after injection of lipopolysaccharides, and the phase of depressive symptoms, which is 24 hours after injection, for cytokines, cyclooxygenase enzymes and mRNA transcription of cytokines. During the sickness behavior, IL-1β and IL-6 were elevated in the blood, IL-1β was elevated in the CSF, and TNF-α was elevated in the striatum of the brain. Also, IL-1β mRNA transcript was increased in the frontal cortex and hippocampus. Curiously, in this phase, IL-6 and COX enzymes were decreased in the hippocampus. After 24 hours of injection, the rats did not show signs of sickness but began displaying depressive symptoms in the forced swim test. This test is used on rodents to evaluate depression and is used when assessing antidepressant drugs and therapies. During the depressive phase of behaviors, the transcription of TNF-α mRNA, IL-6 levels and COX enzymes levels shifted back to normal levels in all brain areas, but the cytokine IL-1β was still significantly elevated in the frontal cortex and hippocampus and there was an increase in the concentration of IL-1β in the cerebral spinal fluid. This increase was only found in the CSF and not in blood serum. This may explain why studies measuring the serum level of cytokines in patients with major depressive disorder, did not find any significant difference when comparing depression levels with normal levels. In this study, they found that Lipopolysaccharide-induced depression is primarily associated with the increase of IL-1β. This cytokine remains elevated in the brain even after the initial inflammatory phase and continues to contribute to a depressive-like phenotype in the rats. This suggests that a short term immune inflammatory response may lead to long term changes in transcription of inflammatory markers and that transcription levels may even increase after the initial immune response (Bay-Richter, Janelidze, Hallberg, & Brundin, 2011).

Although, elevated inflammatory markers are found in many patients with psychiatric disorders, there is no clear differentiation or explanation why some patients have elevated cytokine concentrations and some do not. Perhaps, there is a specific subgroup of patients that will display signs of inflammation. To advance and investigate if the phenomenon of increase cytokine concentrations in psychiatric patients is specific to a subgroup of depressed patients, Janelidze, Mattei, Westrin, Traskman-Bendz, & Brundin (2011) designed a study dividing their subjects by non-suicidal and suicidal patients. In this study, they compared plasma cytokine levels in 47 treated and untreated patients with depression that had attempted suicide, 17 untreated patients with a diagnosis of major depressive disorder that did not have any suicidal ideation and 16 somatically healthy controls with no current or previous history of neuropsychiatric disorder. They found statistically significant elevated plasma concentration of proinflammatory cytokines IL-6 and TNF-α and decreased plasma concentrations of anti-inflammatory cytokine IL-2 in the suicide attempters, compared to the non-suicidal depressed patients and healthy controls. Elevated cytokines were seen in suicidal patients, regardless if they had received treatment or not. Although a limitation of this study is that the duration of the disorder and duration of treatment were not considered. Interestingly, these patients with elevated cytokines did not show any signs of systemic or local

infection or inflammation. This suggests that inflammation seen in depressed patients is specific to those that are suicidal, although it may also be specific to different subgroups of depression too. Furthermore, it suggests that these elevations are associated and may contribute to suicidal ideation. Because this study used patients with untreated major depression, one group it did not control for specifically, is patients with treatment-resistant depression, and therefore, perhaps increased cytokines is seen in all patients with treatment-resistant depression, not only those who have attempted suicide. Evidence of abnormal cytokine elevations were observed in suicidal patients, compared to non-suicidal depressed patients and healthy controls, and may contribute to suicidality.

As the mechanism that causes depression and suicide is located in the brain, it is important to understand if these systemic inflammatory changes relate to changes in the central nervous system. Lindqvist et al. (2009) tested the proinflammatory cytokine profile of the cerebral spinal fluid (CSF) of 63 institutionalized patients who had recently attempted suicide compared to healthy controls. They also evaluated if there was a difference in the cytokine profile of patients who had attempt a violent method of suicide compared to the patients who used a nonviolent method. The patients underwent a "wash-out" period where they discontinued all antidepressant and antipsychotic medication until there was no trace of it in their blood. Depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) and suicidal ideation was assessed using the Suicide Assessment Scale (SUAS). They found that the patients who had attempted suicide had higher levels of cytokine IL-6 in their cerebral spinal fluid to healthy patients, and the violent suicide attempters had the highest concentration of IL-6. They also found that CSF IL-6 had a positive correlation with intensity of depressive symptoms in all suicidal patients. Additionally, they found that IL-6 levels correlated positively with current suicidal ideation and suicidal symptoms, as in patients expressing a "wish to die" and "preoccupation with suicidal thoughts." These results suggest that, as discussed previously, IL-6 may have specific relevance to suicide. They did not find any significant difference in proinflammatory cytokine IL-1β, TNF-α, and IL-8 between the groups studied. Lindqvist et al. then went further to try to determine a mechanism of how these abnormalities may contribute to suicidality. They compared levels of cytokines with known biomarkers of depression and suicide and found that both IL-6 and TNF-α was related to increased levels of 5-HIAA, which is a metabolite of serotonin, and HVA, which is a metabolite of dopamine, in the fluid of the patients who attempted violent suicide methods. This suggests that proinflammatory cytokines may modulate monoamines in the central nervous system. Further, longitudinal studies would be helpful in studying the effects of cytokine and monoamine fluctuation and its neuropsychiatric effects. In summation, Lindqvist et al. found that inflammatory cytokines were directly correlated with the presence and extent of suicidal thought and behavior and the degree of violence of a suicide attempt.

Vitamin D and Depression

As discussed previously, there is strong evidence that vitamin D deficiency may be contribute and cause immune system dysfunction, including elevated inflammatory markers. And elevated inflammatory markers may play a role in depression with suicidal ideation. Therefore, there are many that suggest that vitamin D deficiency may be a contributing factor in those who suffer from suicidal thoughts accompanying major depressive disorder.

The presence of vitamin D receptors (VDR), in the central nervous system was first discovered in 1982 by Stumpf, Sar, Clark, and DeLuca. And nowadays, there is significant evidence of vitamin D's presence and actions on different parts of the brain and nervous system functioning. There is increasing evidence that the vitamin D receptor (VDR) mediates transcription of more than 1,000 genes (Umhau et al., 2013). Calcitriol is known to function in the regulation of neurotransmitters, specifically dopamine, adrenaline, noradrenaline and acetylcholine, regulates several neurotrophic factors of the central nervous system, by enhancing nerve growth factor (NGF) and glial derived neurotrophic factor (GDNF), and assist with anti-oxidative properties in the brain (Humble, 2010). Many of the effects that vitamin D has on the brain, share pathways with factors, when abnormal, are known to be associated with several neuropsychiatric disorders including major depressive disorder (Humble, 2010). Based on this, inadequate levels of vitamin D may lead to changes in the central nervous system that may interfere with brain function and contribute to mood disorders.

As depression is underdiagnosed in non-institutionalized healthy populations and subclinical depression and chronic low mood is common in older adults, and is a factor in morbidity, mortality and quality of life, one study seeking to clarify if vitamin D may be associated with depression in healthy adults was done by Lee et al. (2011). Lee et al. used baseline data from the European Male Ageing Study (EMAS), a cohort study of male aging in Europe, to determine whether concentrations of serum 25-hydroxyvitamin D were associated with levels of depression in a large sample size of 3151 subjects, well-characterized, community-dwelling sample of middle-aged and older men with a mean age 60 ± 11. Subjects were assessed on social issues, lifestyle behaviors, and any related comorbidities, like heart conditions, pituitary disease, diabetes, and cancer. Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II). Their results found that serum vitamin D concentrations were significantly lower in men with depressive symptoms, scoring ≥14 on the

BDI-II, 10 nmol/L decrease in 25-hydroxyvitamin D was associated with an average increase of 5.2% in the BDI-II score. Even after adjusting for age, smoking, alcohol consumption, physical activity, BMI, comorbidities and adverse life events, there was still a significant difference in serum vitamin levels. Additional adjustment for season did not change this inverse association. Only 22 men (0.7%) reported taking vitamin D supplements and exclusion of these men did not change the results. A major limitation of this study, is its difficulty in assessing causality or even if vitamin D contributes to depression. It may be that vitamin D insufficiency may just be a 'risk marker' of general poor health and lifestyle. Depressive behaviors of decreased physical activity and exposure to sunlight may by itself lead to lower vitamin D levels. Lee et al. did attempt to adjust for this factor by assessing if physical activity can contribute to low vitamin D levels but this adjustment does not measure sunlight exposure or rule out reverse causality. The main strengths of this study is their large sample size of healthy subjects of similar origin and uniform methods of assessing depressive symptoms. Their study did find an inverse relationship between serum vitamin D levels and depressive symptoms, mostly independent of confounding factors.

To further this relationship and see if low vitamin D levels is a conclusively a predisposing factor of suicide, Umhau et al. (2013), did a case-control study of 25-hydroxyvitamin D concentration, of serum samples stored in the Department of Defense Serum Repository, of deployed active-duty service members who had subsequently committed suicide. 495 subjects were selected from the Armed Forces Health Surveillance Center (AFHSC) who had officially verified suicides occurring between 2002 and 2008 and had blood sampled within 24 months of death. Controls were randomly selected from the same data bank, and were matched as taking the blood work within 12 months of those who had committed suicide, to minimize for any temporal changes in military environment. They found an increased risk of suicide in lower levels of serum 25-hydroxyvitamin D, and all those who committed suicide has a seasonally adjusted levels below 20 ng/mL. Additionally, they found that 30% of the suicides assessed occurred in those in the lowest levels of vitamin D status. When they graphed the data, they found a curve that is characteristic of nutritional intake, which appears to have benefit until a threshold is reached and after that, any additional enrichment shows little benefit. Meaning, that if sufficient nutrient input is reached then further input will have no effect on outcomes. Which is important when considering Vitamin D supplementation as a treatment method, as discussed later. One limitation of this study, is that vitamin D levels were not measured at the time of suicide but sometimes months before. This problem is lessened by the fact that vitamin D levels are shown to be correlated up to 3 years apart. Perhaps, active-duty service members may have a higher risk of suicide because they often work at night and are excessively covered up in the daytime, therefore, their reduced sun exposure and subsequent reduced vitamin D synthesis contributes to their suicidality. In this study, vitamin D status before suicide attempt was inversely correlated with suicide risk in a large sample size of a specific subset of the population with a general high risk of suicide.

Suicidal ideation may be sudden and in most cases, the first thoughts of suicide often occur less than 10 minutes before the suicide attempt. In a young, and somewhat aggressive, population like military service members, impulsivity may contribute to their risk of suicide. There seems to be a link between vitamin D and impulsivity, as vitamin D increases proinflammatory cytokines in the brain. Proinflammatory cytokines reduces serotonin activity which is long associated with impulsive suicide (Umhau et al.,2013). As discussed in detail earlier, perhaps, this effect of vitamin D is the mechanism by which vitamin D deficiency contributes to higher suicide rates.

Is present vitamin D concentration associated with suicide attempt? As a similarly designed study discussed previously, done by Janelidze, Mattei, Westrin, Traskman-Bendz, & Brundin (2011) to show that increased inflammatory cytokine concentration of IL-6 and TNF-α contributes to suicide risk, Grudet, Malm, Westrin, & Brundin (2014), takes it a step further, to see if vitamin D concentrations, which also contributes to increased inflammatory cytokine concentrations, differ in suicidal depressed patients compared to non-suicidal depressed patients. They included a total of 59 patients who had attempted suicide, and had two control groups of 17 untreated patients with major depressive disorder who had no suicidal ideation and 14 somatically and psychiatrically healthy patients. They found a significant difference in serum 25-hydroxyvitamin D levels between groups, with the suicide attempters have a significantly lower mean vitamin D concentration, of 47 ± 20 nmol/L, than the non-suicidal patients, 62 ± 27 nmol/L, and healthy patients, 65 ± 26 nmol/L. Additionally, 58% of patients in the suicidal group had a clinical vitamin D deficiency of below 50 nmol/L, compared to 30% in the other two control groups. When comparing vitamin D levels and inflammatory cytokines in all groups, they found a correlation between 25-hydroxyvitamin D serum concentrations and proinflammatory cytokine serum concentration of IL-1β. They did not find a statistically significant correlation between vitamin D and cytokines IL-6 and TNF-α in all groups. When comparing individual groups, they found an inverse association between 25-hydroxyvitamin D and IL-1β in the patients who attempted suicide and an inverse association between 25-hydroxyvitamin D and IL-6 in the non-suicidal depressed patients. In conclusion, they found a negative correlation between vitamin D levels and suicide risk and a negative correlation between vitamin D levels and proinflammatory cytokines. The cross-sectional design of

this study does not allow any conclusions whether low vitamin D status can be a direct contributing factor of suicide, but based on previous knowledge of the mechanism of 1,25-dihyroxyvitamin D on brain function and regulation, there is considerable evidence to suggest a direct causality.

Vitamin D deficiency is common in the modern world and Vitamin D supplementation is relatively inexpensive nutritional additive. If this vitamin D insufficiency has a direct contribution on depression and suicide, can vitamin D be used a treatment to reduce depressive symptoms and stop the epidemic of depression and suicide worldwide?

As a vitamin D intake is an easy nutritional therapy, Bertone-Johnson et al. (2011) seeks to clarify if vitamin D supplementation can prevent or treat depression. They patients used for this study were part of a large and diverse sample size that was tracked for a long period of time. The subjects used for this study were part of the observation study (OS) component of the Women's Health Initiative (WHI) This is a database composed by the National Institute of Health which allowed Bertone-Johnson et al. to follow the health of 81,189 postmenopausal women over an 8-year period. Baseline intake was assessed by asking patients about diet and any vitamin D supplementation and estimates of total solar irradiance was calculated based on the geographic location of the clinic centers and controlled when interpreting the results. At each clinic visit, depressive symptoms were assessed using the Burnam 8-item scale for depressive disorders. When controlling for confounding factors, they found that lower vitamin D intake of <100 IU/day had a strong inverse correlation in women who met criteria for prevailing depressive symptoms at the baseline visit. And the reverse was also true, those patients with a substantial intake of vitamin D was associated with a lower prevalence of depressive symptoms. This effect seemed to have a threshold, as those positive effects of increased intake was only shown in patients who consumed 400 to <800 IU/day and an intake of ≥800 IU/day was not associated with decreased risk of depression. At year 3 of the study increased vitamin D intake was correlated with lower risk of depressive symptoms in patients with no evidence of depression at baseline. A limitation of this study, is that it did not measure serum 25-hydroxyvitamin D levels in conjunction with intake levels. This is important as the effects of vitamin D intake on serum vitamin D levels may differ in individuals. Individuals may differ in the processing of vitamin D ingestion; these differences are in part because of genetic factors, vitamin D metabolism and general dietary intake. This study saw an inverse relationship between vitamin D intake and depressive symptoms in older women.

One study, looking at the direct effects of vitamin D supplementation on depressive symptoms in conjunction with metabolic profiles, c-reactive protein (CRP), an inflammatory marker, and oxidative stress. Sepehrmanesh et al., (2016) performed a randomized, double-blind, clinical trial in performed in Kashan, Iran, from October 2014 to December 2014. They included 36 patients, ages 18–65 years, equal parts men and women, diagnosed with major depressive disorder and randomly assigned 18 of them to receive a single capsule of 50,000 IU vitamin D weekly and 18 patients to receive a placebo weekly for 8 weeks in total. The Beck Depression Inventory (BDI) was used to assess depressive symptoms before and after supplementation. As expected, after 8 weeks, changes in vitamin D concentrations were greater in the vitamin D group than in the placebo group. The group taking vitamin D supplements had improved insulin function and decreased oxidative stress than the patients that took a placebo. No changes were seen in c-reactive protein levels between both groups. This may be because of the duration of the study or the specific inflammatory marker studied, as different inflammatory markers have been found to be associated with vitamin D deficiency and depression. But most importantly, this study found that the patients taking vitamin D supplements had significant decreased depressive symptoms, and decreased BDI total scores, post-nutritional therapy compared to before. As all these patients had vitamin D deficiency of less than 20 μg/L at the start of this study, it is not possible to assess if the effects of supplementation are seen only in vitamin D deficient individuals or this therapy may also be useful in those who have clinically sufficient levels of vitamin D. Perhaps the beneficial effects of supplementation can be explained by the fact that both groups had a low baseline mean serum 25-hydroxyvitamin D level. Therefore, a relatively short supplementation period was effective in lowering depressive symptoms. Overall, vitamin D supplementation had a positive effect on lowering depressive symptoms in patients with major depressive disorder.

Conclusion

Vitamin D status seems to be directly linked to mood disorders and particularly major depression. A mechanism for this association is demonstrated in detail, as both are correlated to inflammatory cytokine status. Vitamin D deficiency is associated with an elevation of proinflammatory cytokines because vitamin D modulates and prevents uncontrolled inflammation systemically and in the central nervous system. This elevation of proinflammatory cytokines may have adverse psychiatric effects. It can contribute to depressive symptoms and even suicide. Patients with suicidal thoughts specifically, seem to have abnormal proinflammatory cytokines and lower levels of vitamin D in their body, than patients with major depression that do not have suicidal thoughts.

As the conceptual understanding of vitamin D's activity as a neuro and immune modulator on the brain is an innovative and relatively new area of study, there are few direct-link studies on how the supplementation of vitamin D may reduce instances of major depressive disorder and suicide risk. Vitamin D supplementation treatment for major depressive disorder should be tested in a larger sample size, in patients with clinically sufficient vitamin D status, and for longer periods of time. Additionally, this treatment should be tested in patients with suicidal ideation, as this is the subgroup that has been differentiated to be effected most by vitamin D deficiency. Furthermore, studies should assess the difference between treatments that raise vitamin D levels by intake versus UV ray exposure. Perhaps, vitamin D status and its effects may differ when synthesized naturally in the skin with direct access to subcutaneous fat for storage and the bloodstream, in contrast the supplementation being first processed in the gastrointestinal tract. Vitamin D as a treatment method for major depressive disorder is a new and exciting area of research that may impact the global population tremendously due to the large number of people suffering of depression worldwide. More research on the effectiveness and limitations of this treatment should be done to maximize its impact.

References

Bay-Richter, C., Janelidze, S., Hallberg, L., & Brundin, L. (2011). Changes in behaviour and cytokine expression upon a peripheral immune challenge. Behavioural Brain Research, 222(1), 193-199. http://dx.doi.org/10.1016/j.bbr.2011.03.060

Bertone-Johnson, E. R., Powers, S. I., Spangler, L., Brunner, R. L., Michael, Y. L., Larson, J. C., . . . Manson, J. E. (2011). Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. The American Journal of Clinical Nutrition, 94(4), 1104-1112. http://dx.doi.org/10.3945/ajcn.111.017384

Gardner, A., & Boles, R. G. (2011). Beyond the serotonin hypothesis: Mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35(3), 730-743. http://dx.doi.org/10.1016/j.pnpbp.2010.07.030

Grudet, C., Malm, J., Westrin, A., & Brundin, L. (2014). Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. Psychoneuroendocrinology, 50, 210-219. http://dx.doi.org/10.1016/j.psyneuen.2014.08.016

Hoe, E., Nathanielsz, J., Toh, Z. Q., Spry, L., Marimla, R., Balloch, A., & Mulholland, K. (2016). Anti-inflammatory effects of vitamin D on human immune cells in the context of bacterial infection. Nutrients, 8(12), 806. http://dx.doi.org/10.3390/nu8120806

Humble, M. B. (2010). Vitamin D, light and mental health. Journal of Photochemistry and Photobiology B: Biology, 101(2), 142-149. http://dx.doi.org/10.1016/j.jphotobiol.2010.08.003

Janelidze, S., Mattei, D., Westrin, A., Traskman-Bendz, L., & Brundin, L. (2011). Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain, Behavior, and Immunity, 25(2), 335-339. http://dx.doi.org/10.1037/0002-9432.76.4.482

Johnson, L. E. (2016, September). Vitamin D [Fact sheet]. Retrieved December 27, 2016, from http://www.merckmanuals.com/professional/nutritional-disorders/vitamin-deficiency%2c-dependency%2c-and-toxicity/vitamin-d

Lee, D., Tajar, A., O'Neill, T. W., O'Connor, D. B., Bartfai, G., Boonen, S., & Bouillon, R. (2011). Lower vitamin D levels are associated with depression among community-dwelling European men. Journal of Psychopharmacology, 25(10), 1320-1328. http://dx.doi.org/10.1177/0269881110379287

Lindqvist, D., Janelidze, S., Hagellb, P., Erhardt, S., Samuelsson, M., Minthon, L., & Hansson, O. (2009). Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biological Psychiatry, 66(3), 287-292. http://dx.doi.org/10.1016/j.biopsych.2009.01.030

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biology Psychiatry, 65(9), 732-741. http://dx.doi.org/10.1016/j.biopsych.2008.11.029

Peterson, C. A., & Heffernan, M. E. (2008). Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. Journal of Inflammation, 5(10). http://dx.doi.org/10.1186/1476-9255-5-10

Sepehrmanesh, Z., Kolahdooz, F., Abedi, F., Mazroii, N., Assarian, A., Asemi, Z., & Esmaillzadeh, A. (2016). Vitamin D supplementation affects the Beck Depression Inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: A randomized, controlled clinical trial. The Journal of Nutrition, 146(2). http://dx.doi.org/10.3945/?jn.115.218883

Stumpf, W. E., Sar, M., Clark, S. A., & DeLuca, H. F. (1982). Brain target sites for 1,25-dihydroxyvitamin D3. Science, 215(4538), 1403-1405. http://dx.doi.org/10.1126/science.6977846

Timms, P. M., Mannan, N., Hitman, G. A., Noonan, N., Mills, P. G., Synder-court, D., & Boucher, B. J. (2002). Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: Mechanisms for inflammatory damage in chronic disorders? QJM, 95(12), 787-796. http://dx.doi.org/10.1093/qjmed/95.12.787

Tiwari, S., Pratyush, D. D., Gupta, S. K., & Singh, S. K. (2014). Vitamin D deficiency is associated with inflammatory cytokine concentrations in patients with diabetic foot infection. British Journal of Nutrition, 112(12), 1938-1943. http://dx.doi.org/10.1017/S0007114514003018

Umhau, J. C., George, D. T., Heaney, R. P., Lewis, M. D., Ursano, R. J., Heilig, M., . . . Schwandt, M. L. (2013). Low vitamin D status and suicide: A case-control study of active duty military service members. PLOS ONE. http://dx.doi.org/10.1371/journal.pone.0051543

Vitamin D: Fact sheet for health professionals [Fact sheet]. (2016, February 11). Retrieved December 26, 2016, from https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/