Vitamin D and mental health: The role of the sunshine vitamin

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Abstract

The importance of vitamin D in physical disorders has been well documented. Deficiency in this vitamin is associated with a wide range of physical and mental disorders that include, heart problems, hypertension, stroke, diabetes, various cancers, and asthma. In mental health vitamin D deficiency is associated with schizophrenia, depression, anxiety, Alzheimer’s disease among others. Risk factors for vitamin D deficiency include darker skin, lack of adequate sun exposure, autoimmune diseases, influenza, old age and the use of certain medicines like anticonvulsants. Vitamin D is likely to play an important role in the management and prevention of various mental health problems. In particular, adequate vitamin D during the perinatal stage is likely to impact positively on the long term mental health of a person.

Introduction

Until recently, the importance of Vitamin D, nicknamed “the sunshine vitamin,” has not been fully appreciated with its relative importance only focusing on adult bone health (Holick 2005). However, current estimates suggest that over a billion people have either vitamin D insufficiency or deficiency (Holick 2007). Scientific evidence is mounting implicating its importance in a vast array of physical and mental health problems. In physical health, vitamin D deficiency(VDD) is associated with type 1 diabetes (Mathieu *et al.* 2005), cardiovascular diseases (Baz-Hecht and Goldfine 2010), multiple sclerosis (VanAmerongen *et al.* 2004), sleep disturbance, various cancers including colon, breast, prostate and lung (Pearce and Cheetham 2010). It is also associated with asthma, muscular degeneration, auto immune disturbance, hyperparathyroidism, osteoporosis, cell growth modulation, neuromuscular and immune function. Conversely, adequate levels of vitamin D are associated with a reduction of inflammation (Tariq *et al.* 2011), good bone formation, increasing the activities (upregulates) of some gene enzymes like osteocalcin, osteopontin, calbindin 24-hydroxylase among others. In addition, the hormonally active form of vitamin D called calcitriol, reduces the activities of inflammatory markers like

interleukin 1(IL-1) and IL-2. Calcitriol also stimulates cell differentiation, influences muscular function, and stimulates insulin secretion (Tariq *et al.* 2011). Vitamin D also plays a role in mortality and this is clearly underscored by a recent meta- analysis of 14 eligible studies with 62548 participants showing that, VDD is associated with higher incidence of mortality (Zittermann *et al.* 2012). VDD also causes muscle weakness in children and the elderly with affected children having difficulty in standing and walking (Holick 2006) whereas the elderly have increasing sway and frequent falls (Bischoff-Ferrari *et al.* 2009). Clearly, the importance of vitamin D in physical health is self evident and this is true for mental health.

In mental health, VDD is associated with a number of neurodevelopmental and endocrine disorders (Humble, 2010). Ailments include autism, depression, anxiety, schizophrenia, Alzheimer's disease, premenstrual problems, thyroid regulation and sleep disorders among others. Because of the public health importance of Vitamin D, we carried out a selective review of evidence supporting the role of Vitamin D in some mental health disorders.

In particular, the article reviews evidence supporting the role of VDD in serious mental illness as schizophrenia and depression. The article starts by reviewing the epidemiology of VDD before discussing the mechanism underlying Vitamin D manufacture in the skin and its role in neurodevelopment, schizophrenia and depression. Lastly, the implications for nursing and health in general are discussed.

What is Vitamin D?

Vitamin D is a steroid hormone (neurosteroid), meaning it comes from cholesterol precursors and its traditional role is enhancing the absorption and metabolism of calcium and phosphorous in the body. It affects the key biological functions of over 2000 genes in the body responsible for hormone balance, cell growth and immune function. There are at least five known different forms of vitamin D but only Vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol) are clinically relevant. As a steroid hormone, it is formed from a substance in the skin called 7 dehydrocholesterol (7DHC) after skin is exposure to ultra violet beta (UVB) rays.

Intuitively, it is appealing that people living in sunny climates have sufficient Vitamin D levels but evidence suggest otherwise. Studies carried out in sunny climates like Hawaii, Turkey, India, Iran and Saudi Arabia show that there is a high prevalence of VDD in people living in these countries. The deficiency is almost similar to those living in high latitudes countries (Binkley *et al.* 2007; Lips 2007; Elsammak *et al.* 2011). There is growing tendency for indoor activities by people living in these countries and this partly explains these findings (Fields *et al.* 2011). Moreover, since the 1980's the public has been warned against sunlight exposure to reduce the risk of developing skin cancer and this has played a contributory role in high VDD(Ness *et al.* 1999). In this regard, mental health patients in inpatient settings are at risk of VDD, therefore replenishing this important vitamin is necessary.

Risk factors for vitamin D deficiency

In high latitudes of the Northern hemisphere countries, seasons strongly affect levels of vitamin D in the body. Several studies have found that in these countries, levels of vitamin D decrease during the winter months and increase during summer months (Rapuri *et al.* 2002). Wearing a sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95%.(Matsuoka *et al.* 1987). Patients on a wide variety of medications, including anticonvulsants and medications to treat AIDS/HIV, are at risk because these drugs enhance the breakdown of vitamin D in the body (Zhou *et al.* 2006). In addition to the factors discussed, age is also a risk factor for VDD.

Several studies have found an association between old age and VDD and this is due to atrophic changes of their skin which decreases their capacity to produce adequate amounts of vitamin D (Hirani and Primatesta 2005). Moreover, the capacity for humans to absorb dietary vitamin D through the gut diminish with age(Huotari and Herzig 2008). A study that examined the levels of vitamin D in older people (average age 69years) in Guatemala found that despite living in optimal climate for vitamin D, older Guatemalans had suboptimal levels of vitamin D(Sud *et al.* 2010). This finding is in line with a UK study found worryingly low levels of vitamin D in old people of 65years or over (Hirani and Primatesta 2005). A further recent study found decreased Vitamin D level in older people in nursing homes (Verhoeven *et al.* 2012). By extrapolation, elderly people with mental health problems are equally at risk of VDD. VDD is also common in people with darker skin.

Consistent evidence exist clearly linking VDD and skin colour(Rockell *et al.* 2005; Rockell *et al.* 2008). Some studies in the USA have found that African-Americans are eight times more likely to be vitamin D deficient compared to age-matched Caucasians (Harris 2006; Bodnar *et al.* 2007) and this is supported by a more recent study a multiethnic sample of 503 adults(European, Maori, Pacific and Asian) in New Zealand. The study found that amongst these ethnic groups, Asians had the lowest mean Vitamin D levels and Europeans with lighter coloured skin had the highest (Nessvi *et al.* 2011). The main reason why darker skinned people are prone to VDD is darker skin (highly melanised) is less efficient at manufacturing vitamin D

than lighter skin. In addition to skin colour, obesity is also known to be a risk factor for VDD.

There is an association between inadequate Vitamin D levels and obesity (Alemzadeh *et al.* 2008; Sanchez-Hernandez *et al.* 2005; Renzaho *et al.* 2011; Brock *et al.* 2010). A relatively recent systematic review of 14 studies found an association between VDD and obesity related disorders (Renzaho *et al.* 2011) and another study found a relationship between VDD and BMI index of above thirty (Brock *et al.* 2010). It is also known that obesity is a common problem in people with mental health ailments, therefore, VDD is likely to be prevalent in this population(Phelan *et al.* 2001). More importantly, emerging evidence suggest a link between VDD and the aetiology of various mental health problems such as schizophrenia, depression, Alzheimer's disease and anxiety. Specifically, there is a strong link between vitamin D and neurodevelopmental ailments. This is particularly provocative as we now consider a number of psychiatric illnesses neurodevelopmental in origin. For this reason, it is important to review evidence that support the link between VDD and neurodevelopment.

Vitamin D and neurodevelopment

The discovery of vitamin D metabolites in the cerebrospinal fluid offered the first direct clue of its functional role in the nervous system(Balabanova *et al.* 1984). Evidence from animal models suggests that *in utero* VDD leads to dysregulation of cell differentiation in the developing neonate rat brain. Maternal VDD effect on neonate brain development persist into adulthood even if sufficient vitamin D levels are restored after birth (Feron *et al.* 2005). Further evidence supporting VDD in brain function is the discovery of Vitamin D receptors in the brain of both rodents (Stumpf and O'Brien 1987)and human brain(Eyles *et al.* 2005).

Vitamin D receptors (VDR) start to function as early as the 12th day of gestation and this coincides with the formation of dopamine neurons, a neurotransmitter implicated in psychiatric disorders such as schizophrenia and depression. VDR are involved in the differentiation of many brain areas throughout gestation (Cui *et al.* 2007). Furthermore, there is evidence suggesting VDR is involved in natural cell elimination (Ko et al., 2004). In addition, Vitamin D modulates nerve growth factors (NGF)

essential for the growth and survival of many neurons in the brain. Specifically, the cholinergic basal forebrain neurons are affected (Brown *et al.* 2003). This finding is in line with an earlier animal study that found that injecting vitamin D in ventricles of the brain induces nerve growth factor expression in the hippocampus of adult rats(Saporito *et al.* 1993). These findings have implications for pregnant women in human where an estimated 40% to 80% of pregnant women are vitamin D deficient. This VDD which has ramifications for subsequent brain function is more pronounced in dark skinned ethnic populations living at high latitudes countries. In combination with other factors, VDD during peri-natal life may establish a poor foundation that may produce long-term threats to human health that include risk for developing schizophrenia.

Schizophrenia and vitamin D

We now accept that schizophrenia is a heterogeneous disorder in which genetic and environmental factors interact to contribute to the person's risk for developing the disorder (Eyles *et al.* 2009). To date, evidence linking VDD and schizophrenia is the tendency for people with schizophrenia to be born in the winter months or in higher latitudes countries (Torrey *et al.* 1997; Davies *et al.* 2003). In a review of 250 studies covering 29 Northern and five Southern Hemisphere countries, Torrey et al (1997) found an excess of people with schizophrenia and depression to be born in winter/spring months. This excess was not seen in other mental health disorders. The investigators concluded that, statistical artefact and parental procreational habits are insufficient explanations for this excess, which was as high 8%. In darker skinned individuals living in high latitudes countries, VDD assumes a greater importance as there is a high and disproportionate number of people with schizophrenia in this population (Fearon *et al.* 2006).

More specifically, the relative risk of developing schizophrenia is higher in second than first generation darker skinned migrants who move to high latitude climates(Cantor-Graae and Selten 2005; Dealberto 2010). Because their vulnerability for VDD, darker skinned individuals increase the likelihood of VDD in their offsprings. This hypothesis is supported by several studies including one study that examined maternal VDD as a risk factor for schizophrenia in offsprings using banked maternal sera(McGrath *et al.* 2003). The study found that the offspring of

darker skinned mothers were more likely to develop schizophrenia if the mother had significantly low vitamin D levels especially in the third trimester of pregnancy. By contrast, the chances of the offspring developing schizophrenia were significantly reduced if their mothers had normal vitamin D level during the same period of pregnancy (McGrath et al 2003).

A study that provided direct evidence of the relationship between VDD and the risk of developing schizophrenia is the Northern Finnish cohort study(Ko *et al.* 2004). The study found a reduced risk of developing schizophrenia in male offspring who received adequate vitamin D supplementation than males who did not in their first year of life. This finding is supported by a relatively recent study that examined the link between neonatal vitamin D status and risk of schizophrenia (McGrath *et al.* 2010). The study assessed the concentration of Vitamin D from neonatal dried blood samples of individuals with schizophrenia and controls. Low or very high levels of vitamin D were associated with a risk for developing schizophrenia, suggesting a non linear relationship. Overall, VDD appear to a have a link in mental health disorders like schizophrenia and depression.

Depression

Evidence supporting the role of vitamin D in depression comes from three main sources namely, animal models, epidemiological and, randomised controlled studies. In animal models, mice lacking vitamin D receptor functioning show behavioural impairment that include, memory, perseverative responses and hypolocomotion and these behaviours are seen in hums with depression. Rodents with VDD show dysfunctional noradrenalin gene expression. In humans, noradrenaline is implicated in depression therefore lending indirect evidence for the role of vitamin D in depression. Animal studies also suggest a role for vitamin D in neuroprotection against the effects of dopamine toxins such as methamphetamine. Like noradrenaline, dopamine is implicated in depression (Cass *et al.* 2006). Cass et al (2006) exposed rats to the dopamine toxin, methamphetamine and the rats experienced a significant decrease in serotonin and dopamine concentration in the brain but rats treated with vitamin D did not demonstrate these effects. Cass et al(2006) study is compatible with an earlier finding that showed an increase in dopamine in the cortical region of the brain in rats that were fed a vitamin D replete diet compared to rats on VDD diet(Baksi and Hughes 1982). In people with

depression, both dopamine and serotonin levels are depleted. Taken together, animal studies support the vitamin D hypothesis of depression. In this regard, several epidemiological studies also lend credence to this hypothesis (Hoogendijk *et al.* 2008; Jorde *et al.* 2006; Ganji *et al.* 2010).

Ganji et al (2010) found that those with low Vitamin D blood serum levels were nearly twice as likely to develop depression that those who had higher levels. By far, the strongest evidence supporting a causal link between depression and VDD comes from randomised controlled trials (Jorde *et al.* 2008). In a double blind randomised controlled trial of 441 participants, Jorde et al (2008) compared the outcome of depression in three groups(two groups taking vitamin D of different strengths and one taking placebo). At one year, they found that those with low levels were significantly more depressed than those with adequate levels of vitamin D. Overall, the groups receiving vitamin D supplementation had improved depressive symptoms than those who received placebo. This finding among others has considerable implications for future public health and mental health nursing in particular.

Implication for clinical practice

Studies have demonstrated a clear link between VDD and mental health and its role as a therapeutic agent has attracted considerable interest. From a public health perspective, the use of vitamin D has the potential to alter health care in general and mental health nursing in particular. Vitamin D levels can be increased using inexpensive and well tolerated dietary supplements. In physical health, studies have demonstrated modest improvement in people who take vitamin D supplements towards health. Evidence suggest that taking vitamin D by older people has positive multiple outcomes including reduced falls, higher bone mineral density, and reduced fractures. There is potential therefore for a pivotal role in vitamin D supplementation as part of routine nursing care.

In physical health disorders such as diabetes, the use of vitamin D supplements again shows promising results (von Hurst *et al.* 2010). In a randomised controlled trial that sought to improve the vitamin D status of women who were insulin resistant, Von Hurst et al(2010) found significant improvement in insulin sensitivity and a reduction in fasting insulin in the vitamin D supplementation group compared to

placebo. This finding is likely to find therapeutic application in mental health where a significant proportion of people also have type 2 diabetes.

In depression, this vitamin has the potential to play a useful therapeutic role as demonstrated by a several studies that recorded an improvement in depressive symptoms after vitamin D supplementation. (Hogberg *et al.* 2012; Bertone-Johnson *et al.* 2011). A Norwegian trial of overweight subjects showed that those receiving a high dose of vitamin D (20,000 or 40,000 IU weekly) had a significant improvement in depressive symptoms after 1 year versus those receiving placebo (Jorde *et al.* 2008). From a practical point of view, it is likely that in future, nurses will encourage patients to be exposed to light as part of a treatment plan. It is purported that a light exposure of between 20 to 30 minutes a day is sufficient for the skin to synthesise adequate vitamin. Moreover light therapy for non seasonal affective disorder shows promising results(Tuunainen *et al.* 2004). With regard to schizophrenia, there are currently several randomised controlled trials in process, testing the effect of vitamin D on numerous outcome measures including symptoms and cognition. Clearly, these prospects have the potential to modify nursing practice in future and this may include care for the pregnant.

During pregnancy, the foetus is entirely dependent on the mother for its supply of vitamin D. therefore maternal vitamin D supplementation during pregnancy is necessary and nurses have an important role to play in this regard. Relatively recent Cochrane review has provided evidence on the positive impact of vitamin D supplementation (De-Regil *et al.* 2012). Overall, it is likely that in future vitamin D may play a significant role in public mental health through primary preventative care of neurodevelopmental disorders like schizophrenia.

Conclusion

There is ample biological evidence suggesting the importance of vitamin D in the neurodevelopmental process, physical health and mental health in particular. Current mental health policy emphasises an intergrated approach of physical and mental health care and, this has wider implications for future mental health nursing. Based on the evidence presented in this paper, Vitamin D is likely to have an important role in routine nursing care. From a preventative vantage point, the peri-natal stage of development and care is critical. Good peri-natal care is known to have a positive

and lasting impact on good physical and mental health (Huang 2011). It is likely that nutritional care as a means to promoting good mental health care is likely to be integral in future nursing interventions. In this regard mental health nurses ought to familiarise themselves more with multifunctional role of this important hormone.

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