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Vitamin D and depression

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ABSTRACT

Objective: To examine whether vitamin D deficiency or insufficiency is associated with depression and whether vitamin D supplementation is an effective treatment for depression.

Method: Empirical papers published in recent years were identified using three search engines and online databases – PubMed, Google Scholar and Cochrane Database. Specific search terms used were 'vitamin D', 'depression' and 'treatment' and articles were selected that examined the association between vitamin D deficiency/insufficiency and depression, vitamin D supplementation and Vitamin D as a treatment for depression. Our review weighted more recent studies (from 2011), although also considered earlier publications.

Results: Empirical studies appear to provide increasing evidence for an association between vitamin D insufficiency and depression, and for vitamin D supplementation and augmentation in those with clinical depression who are vitamin D deficient. Methodological limitations associated with many of the studies are detailed.

Limitations: Articles were restricted to those in the English language while publication bias may have weighted studies with positive findings.

Conclusions: There remains a need for empirical studies to move beyond cross-sectional designs to undertake more randomised controlled longitudinal trials so as to clarify the role of vitamin D in the pathogenesis of depression and its management, as well as to establish whether currently suggested associations are clinically significant and distinctive.

1. Introduction

There has been longstanding interest in the role of 'natural' treatments for depression, such as nutritional and dietary products. While many dietary factors have been implicated in the cause and treatment of depression, there has been a lack of scientific rigour in many of the reported studies. The principal dietary preparations so considered in journal reports include omega-3 fatty acids, vitamin D, the vitamin B group, minerals (e.g. zinc, magnesium and iron), antioxidants (e.g. vitamin C) and soy. In this paper we focus on vitamin D as changes in vitamin D receptors impact on various brain neurotransmitters, and thus suggest a potential role of vitamin D in causing and redressing mood disorders. While a role for vitamin D has been implicated in varying psychiatric and neurological conditions, the current review focuses solely on depression.

The aim of this study was to extend a previous 2011 clinical review (Parker and Brotchie, 2011) and include more recent studies evaluating links between vitamin D and depression. In particular, to examine (i) the extent to which vitamin D deficiency and insufficiency is associated with depression, and (ii) whether vitamin D is an efficacious treatment for depression for those with vitamin D deficiency or insufficiency when given as a supplement or when augmenting an antidepressant drug.

2. Methods and material

A literature search of relevant databases was performed (using PubMed, Cochrane Database of Systematic Reviews and Google Scholar) with papers selected that evaluated the association between vitamin D and depression. Specific search terms included "vitamin D" and "depression" – and with "treatment" included to identify studies related to whether vitamin D is an efficacious treatment for depression. In selecting studies, we prioritised those published in recent years (2011–2016) – while also including and overviewing earlier studies - that examined for links between vitamin D deficiency or insufficiency and depression, and as to whether vitamin D has antidepressant properties.

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3. Results

We first detail information regarding the process via which Vitamin D enters the body, consider sufficient and optimal levels in humans and detail the role of vitamin D in the human body. Study results (from the last five years) are considered together with data presented in the previous 2011 review. The section then overviews the empirical research on vitamin D and variable expressions of depression including Seasonal Affective Disorder.

3.1. Overview of vitamin D

Vitamin D can be accessed by humans from a variety of sources, including exposure to sunlight, general diet intake and dietary supplements (Holick, 2007). While there are two types of vitamin D obtained from dietary sources, D_2 (or ergocalciferol) from plant sources (such as mushrooms and soy milk) and D_3 (or cholecalciferol) from animal sources (such as raw fish, mackerel, eel, canned/smoked salmon), D_3 is approximately three times stronger than D_2. However, even from animal sources, it is difficult to obtain sufficient daily vitamin D from general dietary intake (Maxwell, 1994). The majority of vitamin D is produced in the body through the penetration of sunlight on the skin to ultraviolet B (UVB) radiation which involves a complex process involving solar UVB radiation converting 7-dehydrocholesterol to pre-vitamin D_3, and then to vitamin D_3.

Once converted, Vitamin D enters the blood stream and is metabolised in the liver, forming 25-hydroxyvitamin D or 25 (OH) D and is then further metabolised in the kidneys to its active form (1,25-dihydroxyvitamin D). This process is illustrated graphically in Fig. 1. It then binds to vitamin D receptors in target tissues to regulate gene transcription and to structures within cell membranes to mediate a number of non-genomic responses. Vitamin D receptors are present in most tissues and cells in the body, and within the brain show some specificity to the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus and substantia nigra (Eyles et al., 2005, 2013). This is of relevance as many of those brain regions have been implicated in the physiology of depression (Drevets et al., 2008).

Blood levels of 25 (OH) D are used to determine whether an individual has adequate levels of vitamin D and can be reported either as nanograms per millilitre (ng/ml) or as nanomoles per litre (nmol/L). While there is a lack of international consensus, it is generally conceded that the optimal range of 25 (OH) D is between 30 and 60 ng/ml and with 'insufficiency' defined as levels between 21–29 ng/ml and 'deficiency' as < 20 ng/ml (Holick, 2007). For laboratories that measure in nmol/litre, < 50 nM is judged as the criterion for vitamin D deficiency.

Recommendations from the Institute of Medicine of the National Academies (2011) for adequate daily vitamin D levels are 600 IU for children and adults up to 70 years of age, and 800 for adults over 70 years of age. If there is evidence of vitamin D deficiency, the recommended daily supplement is 1000 IU to correct the deficiency and to then maintain adequate levels. It has been estimated that approximately one billion people have insufficient levels of vitamin D or are vitamin D deficient. There are a multitude of reasons for vitamin deficiency, even in warm and sunny climates where vitamin D in the form of sunlight is freely available for most of the year. The season, time of day and latitude affects the amount of solar radiation reaching the skin as the number of solar UVB photons reaching the earth depends on the zenith angle of the sun. Current lifestyle factors also play a role, as the majority of people spend their working hours unexposed to sunshine (Joshi et al., 2010). The elderly may be at particular risk for low levels if housebound or living in nursing homes. Other important factors include ageing, darker skin tones (melanin absorbs more UVB radiation) and sunscreen use – which, while playing an important role in preventing skin cancers, also absorbs UVB radiation. Decreased vitamin D can also occur (i) as a consequence of liver failure and chronic renal diseases, (ii) decreased bioavailability (due to factors such as malabsorption and obesity) and (iii) increased catabolism (due to certain medications, such as anticonvulsants and glucocorticoids).

3.2. Vitamin D and the human body

The potential effects of extended vitamin D deficiency on the human body are vast and varied, and spread across most of the lifespan. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities, and may increase the risk of hip fracture in later adulthood. Vitamin D is considered essential for bone health, and with deficiency potentially leading to calcium deficiency and reduced bone density which can lead to conditions such as osteopenia and osteoporosis. Vitamin D also plays an important role in immunity and in destroying various infectious agents and is judged to have the potential to prevent certain cancers (e.g. breast, colon and prostate). It can also have effects on blood pressure, body circulation and blood sugar control (Holick, 2007).

Eyles et al. (2013) reviewed the biology of vitamin D in the developing and adult brain and the links between low levels of vitamin D and neuropsychiatric diseases. The active form of vitamin D, calcitriol, plays a role in activating the gene expression of an enzyme (tyrosine hydroxylase) which is considered to be the rate-limiting step in the synthesis of the catecholamines. These neurotransmitters (namely, dopamine, noradrenaline and adrenaline) are implicated in the pathophysiology of mood disorders. If there is a causal relationship whereby vitamin D insufficiency or deficiency provides a risk to later depression, suggested possible mechanisms include compromised nerve growth factor synthesis and an impact on various neurotransmitter targets.

3.3. Studies examining for links between vitamin D levels and depression

An overview of the empirical studies examining for an association between vitamin D and depression is now presented, with results described separately for (1) cross-sectional studies, (2) longitudinal studies and (3) randomised controlled trials. The section is concluded by considering a specific subtype of depression - seasonal affective disorder (or SAD) - characterised by depressive symptoms that occur at the darkest time of the year and where it is hypothesised that light deficiency is causal.

3.3.1. Cross-sectional studies

The numerous cross-sectional studies reported in the last decade have generated contrasting findings. A population-based cohort study of those aged 65 years or older in the Netherlands (Hoogendijk et al., 2008) reported that 25 (OH) D levels were 14% lower in both those diagnosed with minor depression (n=169) and with major depression

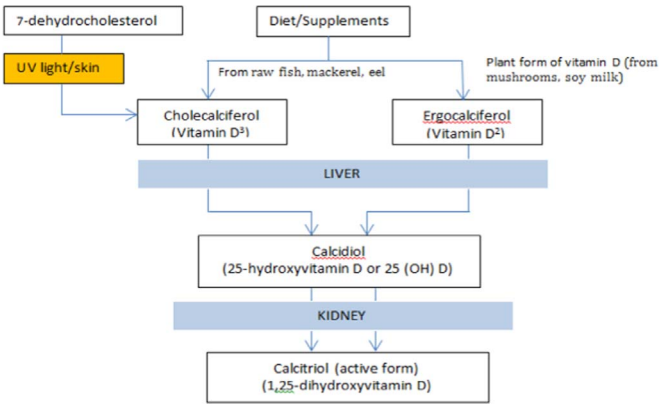

Fig. 1. The metabolism of vitamin D to its active form.