THE IMPORTANCE OF VITAMIN D IN SEASONAL AFFECTIVE DISORDER AND OTHER DEPRESSIVE DISORDERS

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ABSTRACT Seasonal Affective Disorder (SAD) is a form of recurrent depressive or bipolar disorder that is characterized by episodes of major depression that tend to recur during winter usually. Vitamin D is important for serotonin synthesis and low serotonin levels are thought to be associated with depression. During the winter, levels of vitamin D are lower, what might precipitate depression symptoms in individuals with SAD, but it might also be relevant for other depressive disorders, such as major depressive disorder or bipolar disorder. Patients with depression may benefit from vitamin D supplements, especially during the late autumn and winter when sunlight-induced vitamin D production is lower, and diet enriched with tryptophan. Vitamin D supplements may be beneficial in depressed patients with high inflammatory biomarkers because studies have shown that inflammation can produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity. Vitamin D supplements may also improve the efficacy of SSRIs in these patients.

KEYWORDS depression, vitamin D, serotonin, winter

Introduction

Seasonal Affective Disorder (SAD) is a form of recurrent depressive or bipolar disorder, with episodes that vary in severity [1]. Patients that suffer from SAD have episodes of major depression that tend to recur during specific times of the year, usually winter [2]. Studies of brain serotonin function support the hypothesis of disturbed activity. The short-allele polyphorphism for serotonin transporter is more common in patients with SAD than in healthy people [1]. About 5% of USA population experiences SAD, with symptoms present for about 40% of the year. Light therapy during the autumn and winter can be very useful, but should continue through the end of the winter season until spontaneous remission of symptoms in the spring or summer, in order to avoid relapse. Pharmacotherapy (antidepressants) and cognitive behavior therapy are also appropriate treatment options [3].

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The link between vitamin D, serotonin and depression

Serotonin regulates a wide variety of brain functions and behaviors. Brain serotonin is synthesized from tryptophan by tryptophan hydroxylase 2, which is transcriptionally activated by vitamin D hormone [4]. Vitamin D hormone (calcitriol) activates the transcription of the serotonin-synthesizing gene tryptophan hydroxylase 2 (TPH2) in the brain at a vitamin D response element (VDRE) and represses the transcription of TPH1 in tissues outside the blood-brain barrier at a distinct VDRE [5]. Low vitamin D hormone levels during fetal and neonatal development could result in poor gene tryptophan hydroxylase 2 (TPH2) expression and subsequently reduced serotonin concentrations in the developing brain. The important role of TPH2-mediated serotonin production in shaping brain structure and neural wiring during early neurodevelopment is well known [6]. This mechanism suggests that adequate vitamin D hormone levels during pregnancy, as well as nutritional intake of tryptophan and vitamin D during early childhood, may have a critical influence on brain

serotonin levels and thus, on the structure and neural wiring of the brain [5]. Serotonin hypothesis proposes that diminished activity of serotonin pathways plays a causal role in the pathophysiology of depression [7]. The best evidence that serotonin plays a role in the pathophysiology of depression comes from studies of "tryptophan depletion", where an acute dietary manipulation is employed to produce a transient lowering in brain serotonin activity through diminishing availability of its precursor amino acid, tryptophan. In healthy participants with no risk factors for depression, tryptophan depletion does not produce clinically significant changes in mood; however, recovered depressed patients free of medication can show brief, clinically relevant, depressive symptomatology [8]. Inflammation can produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity. Such an effect could explain the diminished efficacy of SSRIs (selective serotonin reuptake inhibitors) in depressed patients with high levels of inflammatory biomarkers [9]. Calcitriol is a well-known endocrine regulator of calcium homeostasis. More recently, local calcitriol production by immune cells was shown to exert autocrine or paracrine immunomodulating effects. Immune cells that produce calcitriol also express the vitamin D receptor (VDR) and the enzymes needed to metabolize vitamin D3 (1α-, 25-, and 24-hydroxylases). Studies of animal models and cell cultures showed both direct and indirect immunomodulating effects involving the T cells, B cells, and antigen-presenting cells (dendritic cells and macrophages); and affecting both innate and adaptive immune responses. The overall effect is a switch from the Th1/Th17 response to the Th2/Treg profile. The immunomodulating effects of vitamin D may explain the reported epidemiological associations between low vitamin D status and a large number of autoimmune and inflammatory diseases. Such associations have been suggested by observational studies not only in rheumatoid arthritis, lupus, inflammatory bowel disease, and type 1 diabetes; but also in infections, malignancies, transplant rejection, and cardiovascular disease. In animal models for these diseases, vitamin D supplementation has been found to produce therapeutic effects [10]. Vitamin D supplements may improve the efficacy of SSRIs in the depressed patients with high levels of inflammatory biomarkers. Patients with autoimmune and inflammatory diseases who suffer from depression may benefit from vitamin D supplementation as well. Vitamin D is thought to increase the level of brain serotonin and thus, opposes the effect of inflammation, which lowers tryptophan and consequently, serotonin levels, which means that optimal vitamin D status positively correlates with optimal serotonin levels.

Light therapy

Observations from clinical trials have frequently demonstrated that light therapy can be an effective therapy for seasonal and non-seasonal major depression. It is known that light therapy modulates mood states and cognitive functions, involving circadian and non-circadian pathways from retinas into brain [11]. SAD is prevalent when vitamin D stores are typically low. Broad-spectrum light therapy includes wavelengths between 280-320 nm which allow the skin to produce vitamin D [12]. Analysis of pooled data from randomized trials provides evidence for the efficacy of use of bright light therapy $\geq$ 5,000 lux for periods $\geq$ 30 minutes when used as augmentation to standard antidepressant pharmacotherapy in the treatment of major depressive disorder and bipolar depression without a seasonal pattern [13].

Conclusion

1. Sun light (spectrum 280–320 UVB) is important for vitamin D3 production. Clothing and sun protection creams, especially with high sun protection factor (SPF) prevent vitamin D3 production in the skin. Vitamin D deficiency is identified as a world global problem with approximately 14% of the population with inadequate vitamin D levels [14]. During the winter, levels of vitamin D are lower and thus, may precipitate depression symptoms in individuals with major depressive disorder or bipolar disorder.

2. Broad-spectrum light therapy that includes wavelengths between 280 and 320 nm, which allow the skin to produce vitamin D, is shown to be useful in patients with SAD, but also in patients with major depressive disorder and bipolar depression without a seasonal pattern.

3. Low serotonin levels are thought to be associated with depression. Serotonin regulates a variety of cognitive functions: mood, decision-making, social behavior, excessive worry and impulse control. Vitamin D is important for serotonin synthesis. Brain serotonin is synthesized from tryptophan by tryptophan hydroxylase 2. Tryptophan hydroxylase is transcriptionally activated by vitamin D hormone. Patients with depression may benefit from vitamin D supplements and diet enriched with tryptophan.

4. Some studies shown that inflammation can produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity. Such an effect could explain the diminished efficacy of SSRIs in depressed patients with high levels of inflammatory biomarkers. SSRIs are considered as a first line treatment for major depressive disorder, as well as for seasonal depression. Patients with autoimmune and inflammatory diseases may have poorer clinical outcome with SSRIs therapy. Vitamin D is known for its immunomodulatory effects and thus, vitamin D supplements may be beneficial in depressed patients with high inflammatory biomarkers. Vitamin D supplements may also improve the efficacy of SSRIs in these patients.

To summarize, it would be rationale to measure levels of vitamin D of every patient that suffers from depression, and to treat vitamin D deficiency if present. Nutritional interventions are very important part of multi-modal therapy for all depressive disorders, which also includes light therapy, pharmacotherapy (antidepressant agents), cognitive therapy, art therapy, work therapy, and spiritual support (for religious individuals). Further pre-clinical and clinical investigation is mandatory in order to better understand the clinical significance of vitamin D status in the context of SAD and other depressive disorders.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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