Metabolic Brain Disease
https://doi.org/10.1007/s11011-019-00486-1

ORIGINAL ARTICLE

Vitamin D supplementation ameliorates severity of generalized anxiety disorder (GAD)

Alaa Eid[1] · Sawsan Khoja[1,2] · Shareefa AlGhamdi[1,2] · Hadeil Alsufiani[1,2,3] · Faten Alzeben[4] · Nasim Alhejaili[4] · Haythum O. Tayeb[5] · Frank I. Tarazi[6]

Received: 27 March 2019 / Accepted: 20 August 2019

Abstract

This study investigated the effects of vitamin D supplementation on Generalized Anxiety Disorder (GAD) clinical symptoms and neurochemical biomarkers including serotonin, neopterin and kynurenine. Thirty male and female patients diagnosed with GAD and had vitamin D deficiency were recruited from the psychiatric clinic at King Abdulaziz University Hospital and divided into two groups; one group of patients ($n = 15$) received standard of care (SOC) plus 50,000 IU vitamin D (once/week) for 3 months, while the other group (n = 15) received SOC alone. Biochemical parameters including serum vitamin D, serotonin, neopterin and kynurenine were measured for all patients enrolled in the trial. In addition, the Generalized Anxiety Disorder 7-item (GAD-7) scale was used to measure the severity of GAD symptoms in both vitamin D treated- and untreated-patients. Significant improvements in GAD scores were observed in the vitamin D-treated group compared to the group that did not receive vitamin D. In addition, serum serotonin concentrations were significantly increased while serum neopterin were significantly decreased in vitamin D-treated vs. untreated patients. In contrast, no significant differences were found in serum kynurenine concentrations at the end of the study period between the two groups. No changes either in GAD-7 scores or in any of the biochemical measurements were observed in the group that received only SOC after 3 months. Vitamin D supplementation was effective in ameliorating the severity of GAD symptoms by increasing serotonin concentrations and decreasing the levels of the inflammatory biomarker neopterin in GAD patients.

Keywords Vitamin D · Generalized anxiety disorder · Serotonin · Neopterin · Kynurenine

✉ Shareefa AlGhamdi
saaalghamdi1@kau.edu.sa

[1] Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

[2] Vitamin D Pharmacogenomics Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

[3] Experimental Biochemistry Unit, King Fahad Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

[4] Division of Psychiatry, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[5] Division of Neurology, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[6] Department of Psychiatry and Neuroscience Program, Harvard Medical School and McLean Hospital, Boston, MA, USA

Introduction

Generalized Anxiety Disorder (GAD) is one of a multitude of anxiety disorders that affect 0.8%–6.4% of world population (Kirmayer 2001; Lieb et al. 2005; Grant et al. 2005; Kessler and Wang 2008). Patients with GAD usually experience long-term anxiety with no obvious reason or external cause (Portman et al. 2012) and exhibit excessive worry, restlessness and concentration difficulty (Hoffman et al. 2008). GAD is often severe enough leading to impairments in daily functioning, including work productivity, social interactions, and self-care (Wittchen and Hoyer 2001).

GAD pathophysiology may encompass psychological, environmental, and neurobiological factors. One of the neurobiological factors that may underlie the pathophysiology of GAD is serotonin (5-hydroxytryptamine; 5-HT) (Ionescu et al. 2013, Berger et al. 2009). Several

Published online: 02 September 2019

studies proposed that imbalances in 5-HT neurotransmission may contribute to the development and persistence of anxiety disorders, including GAD (Eison 1990; Griebel 1995). Lesch and Gutknecht (2005) reported that patients with anxiety disorder have genetic polymorphisms in the 5-HT transporter (5-HT_T) gene. This transporter is located on the plasma membrane of the serotonergic neurons and is responsible for the reuptake of synaptic 5-HT into the neuron (Piñeyro and Blier 1999). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) mediate their clinical antidepressant activities by blocking the presynaptic 5-HT_T and enhancing 5-HT neurotransmission (Stahl 1998). Oxidative stress may also play a role in the neurobiology of anxiety disorders (Boldrini et al. 2018; Gautam et al. 2012; Bouayed et al. 2009, 2011). Sustained stress can promote neuroinflammation and trigger an increase in reactive oxygen species and other markers of neuroinflammation such as pro-inflammatory cytokines, neopterin and kynurenine (Stone 2001; Murr et al. 2002; Kim and Jeon 2018).

Vitamin D is well known for its essential roles in bone metabolism but has been found to also play a role in brain health as a neurosteroid (DeLuca 2004; Groves et al. 2014). Circulating 25-hydroxy vitamin D crosses the blood-brain barrier and enters glial and neuronal cells where it is converted into its active form, 1,25-hydroxy vitamin D (DeLuca et al. 2013). 1,25-hydroxy vitamin D binds to vitamin D receptors (VDRs) found in more than 30 cell types throughout the body, including neurons (Holick et al. 2007). Several recent studies have demonstrated an association between low serum 25-hydroxy-vitamin D concentrations and affective disorders, particularly depression (Hoogendijk et al. 2008; Hoang et al. 2011; Milaneschi et al. 2014; Pu et al. 2018; Hansen et al. 2014; Fedotova et al. 2017; Bicikova et al. 2015). Limited number of studies suggests that vitamin D deficiency may contribute to the expression of anxiety symptoms (Bicikova et al. 2015). Nonetheless, the association between vitamin D deficiency, anxiety and stress is still debated and require further investigation.

This study explored the role of vitamin D deficiency (vitamin D serum levels 25–50 nmol /L) in the pathophysiology of GAD by studying the clinical and biochemical effects of vitamin D supplementation in a sample of GAD patients from Saudi Arabia, a country where both low vitamin D levels and anxiety disorders are prevalent (Al-Daghri 2018, Hariri 2016, Al-Modayfer and Alatiq 2015). We hypothesized that improving vitamin D levels by vitamin D supplementation will ameliorate the severity of GAD symptoms and alter neurochemical biomarkers of anxiety and oxidative stress, including serotonin, neopterin and kynurenine.

Materials and methods

Trial design

The study was approved by the Institutional Review Board and done in accordance with the ethical standards of the Ethical committee of the Faculty of Medicine at King Abdulaziz University. All participants gave written informed consent to enroll in the trial. We recruited 30 adult Saudi patients (ages 18–65 years old) with GAD and vitamin D deficiency (vitamin D level 25–50 nmol/L) from the psychiatric clinics at the King Abdulaziz University Hospital in Jeddah, Saudi Arabia. The study period was from February to November 2017. A board-certified psychiatrist made the diagnosis of GAD according to the criteria of the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM5). We measured serum levels of vitamin D in all subjects and excluded patients with a vitamin D level > 50 nmol/L (vitamin D-replete patients) or < 25 nmol/L (vitamin D-deficient patients who were treated with vitamin D but not included in the study). We also measured baseline serum levels of parathyroid hormone (PTH) and excluded those with abnormal levels of PTH from the study. Patients with other comorbid conditions including major depression, bipolar disorder and substance abuse were also excluded from the study. All enrolled patients received standard of care (SOC) treatment for GAD including antidepressant and anxiolytic medications. We randomized patients into two groups. First group ($n = 15$) received SOC plus 50,000 IU Vitamin D3 (once/week) for 3 months, while the second group (n = 15) received only SOC for 3 months. We recorded demographic data related to each patient, including gender, age, marital status, level of education, smoking status and BMI. The level of education and smoking status were included to reflect the social heterogeneity among the enrolled patients and not as an indicator or a side effect of GAD. We assessed the severity of GAD symptoms using the Generalized Anxiety Disorder-7 item (GAD-7) scale. The GAD-7 total score ranges from 0 to 21, with three levels of severity, mild (5–9), moderate (10–14) and severe (15–21) (Spitzer et al. 2006).

Biochemical measurements

All participants donated fasting blood samples. Serum samples were separated and stored at −80 °C for later measurements of biochemical para meters including vitamin D, serotonin, neopterin and kynurenine. Serum 25-hydroxy vitamin D3 was measured by the electrochemiluminescence immunoassay method using COBAS e411 automated machine analyzer (Roche company, USA). An enzyme-linked immunosorbent assay kit (ab133053- serotonin in vitro competitive ELISA kit) was used to quantitatively determine serum serotonin according to the manufacturer's protocol. Serum neopterin and

kynurenine levels were measured quantitatively by using human Neopterin ELISA kit (cat no. K10554, SingoGeneClon Biotech Co., Ltd) and human kynurenine ELISA kit (cat no. k10619, SingoGeneClon Biotech Co., Ltd), respectively.

Statistical analysis

One-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison test was used to determine whether there were significant differences in GAD7 scores, serum vitamin D, serotonin, neopterin, and kynurenine levels between the SOC + vitamin D group vs. SOC group treatment at baseline and after 3 months. We performed statistical analyses using GraphPad Prism version 6 for Windows, GraphPad Software, San Diego, California, USA. Data are presented as means ± SEM, with p value <0.05 set as the criterion of significance.

Results

Table 1 shows demographic characteristics of study participants and their GAD7 scores. The mean age of enrolled patients (17 males and 13 females) was 40 years. More than 75% of the patients were non-smokers and more than 70% had a BMI above 25 kg/m^2. There was no significant difference between males and females with regard to age, BMI or baseline GAD7 scores. The majority of the participants had moderate to severe anxiety. Baseline GAD7 scores were not significantly different between the group that received SOC + vitamin D vs. the group that received SOC alone (mean scores were 13.6 and 13.8, respectively). Similarly, baseline vitamin D serum levels were indifferent between the group that received SOC + vitamin D vs. the group that received SOC alone (mean levels were 41.7 and 43.5 nmols/L, respectively).

Table 1 Baseline characteristics of study participants

	Mean	SEM
Age (years)	40.1	2.00
Height (cm)	161	2.40
Body mass (kg)	74.8	3.23
	N	%
BMI (kg/m2)		
< 18.9	0	0
19–24.9	8	26
25–29.9	11	37
> 30.0	11	37
Marital status		
Married	21	70
Single	9	30
Level of education		
Early childhood education	6	20
Primary education	5	17
Secondary education	9	30
Collage education	10	33
Smoking status		
Smoker	6	20
Non-smoker	24	80
GAD score		
Mild (5–9)	**4**	**14**
Moderate (10–14)	**17**	**59**
Sever (15–21)	**11**	**38**

At the 3-month follow up visit, the GAD7 scores of the group that received both SOC and vitamin D were significantly decreased (mean = 9.5) compared to their baseline level (mean 13.6; $p < 0.0001$). In contrast, follow-up GAD7 score of the SOC group did not change significantly from baseline (mean = 14.1 vs. 13.8 at baseline; $p = 0.77$) (Fig. 1). The follow-up vitamin D serum levels of the first group expectedly increased in comparison to their baseline level (90.1 mean = nmol/L, $p < 0.0001$), and was significantly higher than that of the SOC group at their 3-month follow up visit (mean = 36.54 nmol/L, $p < 0.0001$) (Fig. 2). In the SOC + vitamin D group, serum serotonin levels significantly increased in comparison to their baseline levels (means 155 and 135 mmol/L respectively, $p < 0.01$). In the SOC group, there was no statistically significant difference between baseline and 3-month follow up visit (means 182.1 and 176.6 mmol/L respectively, $p = 0.94$) (Fig. 3). Serum neopterin concentrations significantly decreased in the SOC + vitamin D group by approximately five folds compared with the baseline levels (means 68 and 12 respectively, $p < 0.001$). On the other hand, the SOC group had higher serum neopterin levels at their follow up visit in comparison to their baseline levels (Fig. 4). In contrast to serotonin and neopterin, serum kynurenine concentrations did not change at the follow up visit in comparison to the baseline levels in both SOC + vitamin D (means 2.2 ± 0.21 and 2.2 ± 0.23, $p = 0.98$) and SOC (means 2.3 ± 0.26 and 2.2 ± 0.31, $p = 0.98$) groups (Fig. 5).

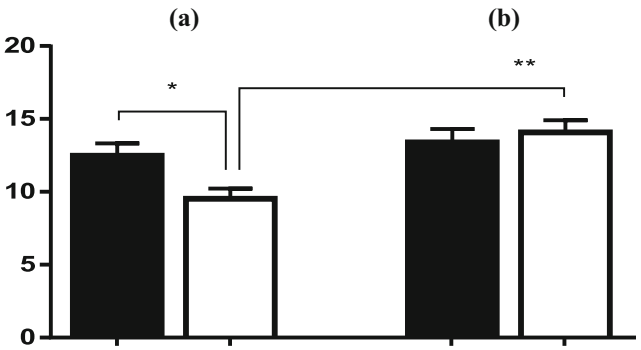

Fig. 1 GAD7 scores in GAD patients. GAD7 scores (mean ± SEM) in (**a**) patients treated with SOC + vitamin D and (**b**) patients treated with SOC alone. Baseline levels are represented by black bars. Follow up levels at 3-months are represented by white bars. *$p < 0.05$, **$p < 0.01$

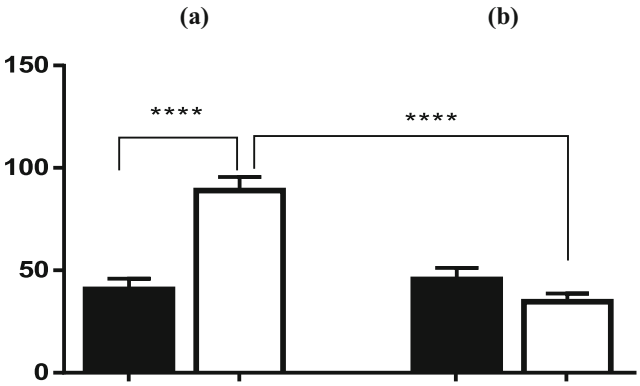

Fig. 2 Serum vitamin D levels in GAD patients. Serum vitamin D levels (mean ± SEM) expressed in nmol/L in (**a**) patients treated with SOC + vitamin D and (**b**) patients treated with SOC alone. Baseline levels are represented by black bars. Follow up levels at 3-months are represented by white bars. ****$p < 0.0001$

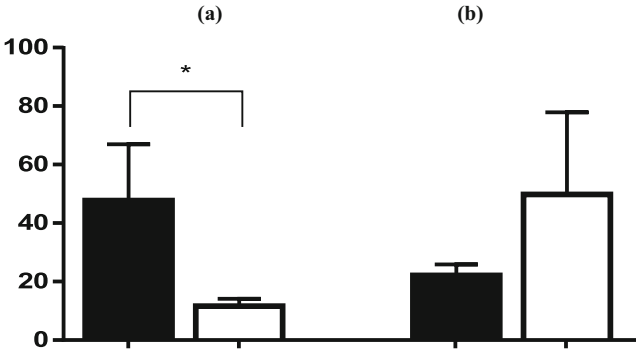

Fig. 4 Serum neopterin levels in GAD patients**.** Serum neopterin levels (mean ± SEM) expressed in nmol/L in (**a**) patients treated with SOC + vitamin D and (**b**) patients treated with SOC alone. Baseline levels are represented by black bars. Follow up levels at 3-months are represented by white bars. *$p < 0.005$

Discussion

The potential role of vitamin D in anxiety disorders has not been adequately investigated. This is in contrast to its role in depression where a large body of research demonstrated an association between low vitamin D levels and depression (Hoang et al. 2011; Bicikova et al. 2015), and showed that vitamin D supplementation improved depressive symptoms (Jorde et al. 2008). This study is the one of the first few studies to investigate the effect of vitamin D supplementation on GAD clinical symptomology, and the first to our knowledge that investigated associated changes in neurochemical biomarkers including serotonin, neopterin and kynurenine in the same patients. The study took place in a population of patients who displayed both GAD symptoms and vitamin D deficiency, raising the question of whether there is an association between them. The results demonstrate that, in the presence of vitamin D deficiency, augmenting SOC of GAD by weekly vitamin D supplementation of 50,000 IU for 3 months significantly reduced the severity of anxiety symptoms. We also demonstrated that the clinical improvement in anxiety symptoms was associated with neurochemical changes that were not detected in the group that received SOC only. Serum serotonin levels increased significantly in the vitamin D-treated vs. non-treated group. This may be mediated through vitamin D established role in activating transcription of the tryptophan hydroxylase-2 gene, leading to increased conversion of tryptophan to serotonin in the brain (Patrick and Ames 2014). Furthermore, our study demonstrates that patients with GAD treated with vitamin D had a reduction in serum levels of neopterin, a mediator of cellular immunity and a biomarker for oxidative stress (which is in turn a potential culprit mechanism of stress, anxiety and neuroinflammation). This supports the hypothesis that vitamin D actions in GAD may be partly mediated through its anti-inflammatory effects that reduce oxidative stress, a mechanism previously suggested to contribute to vitamin D antidepressant effects. Hellmuth and colleagues showed a significant relationship between baseline plasma neopterin and depression scores

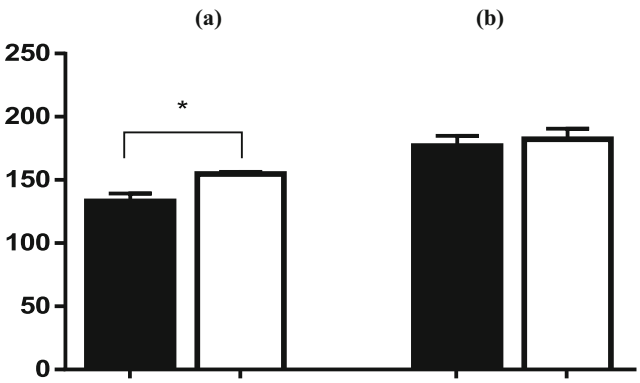

Fig. 3 Serum serotonin levels in GAD patients. Serum serotonin levels (mean ± SEM) expressed in nmol/L in (**a**) patients treated with SOC + vitamin D and (**b**) patients treated with SOC alone. Baseline levels are represented by black bars. Follow up levels at 3-months are represented by white bars. ****$p < 0.0001$

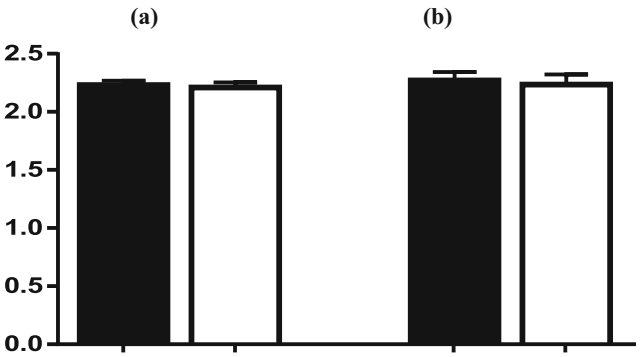

Fig. 5 Serum kynurenine levels in GAD patients. Serum kynurenine levels (mean ± SEM) expressed in nmol/L in (**a**) patients treated with SOC + vitamin D and (**b**) patients treated with SOC alone. Baseline levels are represented by black bars. Follow up levels at 3-months are represented by white bars. ****$p < 0.0001$

(Hellmuth et al. 2017). Our study did not find significant changes in the levels of kynurenine, which contrasts with prior findings in patients with anxiety and depression, requiring further study in a larger group of patients (Kim and Jeon 2018; Maes et al. 2002).

Limitations

The study had several limitations. The lack of placebo control group prevented the definitive conclusion that the observed clinical and neurochemical benefits were solely attributed to vitamin D supplementation. The small number of patients enrolled in the trial might have masked any significant changes in GAD7 scores in non-treatment group. Finally, this trial was conducted in a clinical context, meaning that healthcare providers were permitted to alter SOC according to the clinical necessities of every patient, making it hard to ascertain that this did not confound the comparison between vitamin D-treated and non-treated groups.

Conclusion

This clinical trial demonstrated that augmenting SOC of GAD in vitamin D-deficient patients with vitamin D supplements resulted in significant improvement in GAD symptoms, an increase in serotonin levels, and a reduction in neopterin levels. This study provides clinical and biochemical data that point to a potential neurochemical and therapeutic role for vitamin D in GAD. A larger scale, placebo-controlled clinical trial is needed to validate whether vitamin D is therapeutically beneficial in the improved treatment of GAD.

Acknowledgements The authors are grateful to all patients who participated in the study. The authors also thank the deanship of scientific research (DSR). This work was supported by the deanship of scientific research (DSR)- King Abdulaziz University- Saudi Arabia under Grant [G:209-247-1440].

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

References

Al-Daghri NM (2018) Vitamin D in Saudi Arabia: prevalence, distribution and disease associations. J Steroid Biochem Mol Biol 175:102–107

Al-Modayfer O, Alatiq Y (2015) A pilot study on the prevalence of psychiatric disorders among Saudi children and adolescents: a sample from a selected community in Riyadh city. Arab J Psychiatry 26(2):184–192

Berger M, Gray JA, Roth BL (2009) The expanded biology of serotonin. Ann Rev Med 60:355–366

Bicikova M, Duskova M, Vitku J, Kalvachova B, Ripova D, Mohr P (2015) Starka L (2015) vitamin D in anxiety and affective disorders. Physiol Res 64(suppl 2):S101–S103

Boldrini P, Fusco A, Nicoletti F, Badiani A, Saso L (2018) Potential use of modulators of oxidative stress as add-on therapy in patients with anxiety disorders. Curr Drug Targets 19(6):636–650

Bouayed J, Rammal H, Soulimani R (2009) Oxidative stress and anxiety: relationship and cellular pathways. Oxidative Med Cell Longev 2(2):63–67

Bouayed J, Hoffmann L, Bohn T (2011) Total phenolics, flavonoids, anthocyanins and antioxidant activity following simulated gastro-intestinal digestion and dialysis of apple varieties: bioaccessibility and potential uptake. Food Chem 128(1):14–21

DeLuca HF (2004) Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 80(6):1689S–1696S

DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC (2013) Review: the role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol 39(5):458–484

Eison MS (1990) Serotonin: a common neurobiologic substrate in anxiety and depression. J Clin Psychopharmacol 10(3 Suppl):26S–30S

Fedotova J, Zarembo D, Dragasek J, Caprnda M, Kruzliak P, Dudnichenko T (2017) Modulating effects of cholecalciferol treatment on estrogen deficiency-induced anxiety-like behavior of adult female rats. Folia Med 59(2):139–158

Gautam M, Agrawal M, Gautam M, Sharma P, Gautam AS, Gautam S (2012) Role of antioxidants in generalised anxiety disorder and depression. Indian J Psychiatry 54(3):244–247

Grant BF, Hasin DS, Stinson FS, Dawson DA, June Ruan W, Goldstein RB, Smith SM, Saha TD, Huang B (2005) Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on alcohol and related conditions. Psychol Med 35(12):1747–1759

Griebel G (1995) 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: more than 30 years of research. Pharmacol Ther 65(3):319–395

Groves NJ, McGrath JJ, Burne TH (2014) Vitamin D as a neurosteroid affecting the developing and adult brain. Ann Rev Nutr 34:117–141

Hansen AL, Olson G, Dahl L, Thornton D, Grung B, Graff IE, Froyland L, Thayer JF (2014) Reduced anxiety in forensic inpatients after a long-term intervention with Atlantic salmon. Nutrients 6(12):5405–5418

Hariri A (2016) Vitamin D deficiency/insufficiency and anxiety among Saudis: degree and differences. Euro Scientific J 12(27)

Hellmuth J, Colby D, Valcour V, Suttichom D, Spudich S, Ananworanich J, Prueksakaew P, Sailasuta N, Allen I, Jagodzinski LL, Slike B, Ochi D, Paul R (2017) Depression and anxiety are common in acute HIV infection and associate with plasma immune activation. AIDS Behav 21(11):3238–3246

Hoang MT, Defina LF, Willis BL, Leonard DS, Weiner MF, Brown ES (2011) Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the Cooper Center longitudinal study. Mayo Clin Proc 86(11):1050–1055

Hoffman DL, Dukes EM, Wittchen HU (2008) Human and economic burden of generalized anxiety disorder. Depress Anxiety 25(1):72–90

Holick MF, Chen TC, Lu Z, Sauter E (2007) Vitamin D and skin physiology: a D-lightful story. J Bone Miner Res 22(S2):V28–V33

Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW (2008) Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 65(5):508–512

Ionescu DF, Niciu MJ, Mathews DC, Richards EM, Zarate CA Jr (2013) Neurobiology of anxious depression: a review. Depressi Anxiety 30(4):374–385

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K (2008) Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med 264(6):599–609

Kessler RC, Wang PS (2008) The descriptive epidemiology of commonly occurring mental disorders in the United States. Ann Rev Public Health 29:115–129

Kim Y-K, Jeon SW (2018) Neuroinflammation and the immune-kynurenine pathway in anxiety disorders. Curr Neuropharmacol 16(5):574–582

Kirmayer LJ (2001) Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. J Clin Psychiatry 62:22–30

Lesch KP, Gutknecht L (2005) Pharmacogenetics of the serotonin transporter. Prog Neuro-Psychopharmacol Biol Psychiatry 29(6):1062–1073

Lieb RE, Becker E, Altamura C (2005) The epidemiology of generalized anxiety disorder in Europe. Eur Neuropsychopharmacol 15(4):445–452

Maes M, Verkerk R, Bonaccorso S, Ombelet W, Bosmans E, Scharpé S (2002) Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci 71(16):1837–1848

Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, Beekman AT, Smit JH, Penninx BW (2014) The association between low vitamin D and depressive disorders. Mol Psychiatry 19(4):444–451

Murr C, Widner B, Wirleitner B, Fuchs D (2002) Neopterin as a marker for immune system activation. Curr Drug Metab 3(2):175–187

Patrick RP, Ames BN (2014) Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. FASEB J 28(6):2398–2413

Piñeyro G, Blier P (1999) Autoregulation of serotonin neurons: role in antidepressant drug action. Pharmacol Rev 51(3):533–591

Portman ME, Riskind JH, Rector NA (2012) Generalized anxiety disorder. In: Encyclopedia of human behavior, Second edn. Academic Press, San Diego, pp 215–220

Pu D, Luo J, Wang Y, Ju B, Lv X, Fan P, He L (2018) Prevalence of depression and anxiety in rheumatoid arthritis patients and their associations with serum vitamin D level. Clin Rheumatol 37(1):179–184

Spitzer RL, Kroenker K, Williams JB, Lowe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166(10):1092–1097

Stahl SM (1998) Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord 51(3):215–235

Stone TW (2001) Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. Prog Neurobiol 64(2):185–218

Wittchen H-U, Hoyer J (2001) Generalized anxiety disorder: nature and course. J Clin Psychiatry 62:15–21