ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

REGULAR ARTICLE

Depressed adolescents in a case-series were low in vitamin D and depression was ameliorated by vitamin D supplementation

Göran Högberg (gor.hogberg@gmail.com)[1,2], Sven A Gustafsson[3], Tore Hällström[4,5], Tove Gustafsson[6], Björn Klawitter[2], Maria Petersson[6]

1.Department of Women's and Children's Health, Child and Adolescent Psychiatric Unit, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden
2.Stockholm Child and Adolescent Psychiatry, BUP Huddinge Stockholm, Stockholm, Sweden
3.Department of Molecular Medicine and Surgery, Section of Clinical Chemistry, Karolinska Institutet, Stockholm, Sweden
4.Department of Clinical Neuroscience, Section for Psychiatry, Huddinge, Karolinska Institutet, Stockholm, Sweden
5.Department of Neuroscience and Physiology, Section of Psychiatry and Neurochemistry, Unit for Neuropsychiatric Epidemiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
6.Department of Molecular Medicine and Surgery, Endocrine and Diabetes Unit, Karolinska Institutet, Stockholm,Sweden

Keywords
Adolescent, Depression, Vitamin D deficiency, Vitamin D supplementation

Correspondence
Göran Högberg, BUP Huddinge, Paradistorget 4, 141 47 Huddinge, Sweden.
Tel: +46-514-529-00 |
Fax: +46-514-529-05 |
Email: gor.hogberg@gmail.com

Received
17 December 2011; revised 4 February 2012; accepted 23 February 2012.

DOI:10.1111/j.1651-2227.2012.02655.x

ABSTRACT

Aim: The relationship between depression in adolescents and vitamin D was studied in a case-series that included effects of vitamin D supplementation.

Methods: Serum 25OH vitamin D (25OHD) levels in 54 Swedish depressed adolescents were investigated. Subjects with vitamin D deficiency were given vitamin D_3 over 3 months (n = 48). To evaluate well-being and symptoms related to depression and vitamin D status, the WHO-5 well-being scale, the Mood and Feelings Questionnaire (MFQ-S) and a vitamin D deficiency scale were used.

Results: Mean serum 25OHD in the depressed adolescents was 41 at baseline and 91 nmol/L ($p < 0.001$) after supplementation. Basal 25OHD levels correlated positively with well-being ($p < 0.05$). After vitamin D supplementation, well-being increased ($p < 0.001$) and there was a significant improvement in eight of the nine items in the vitamin D deficiency scale: depressed feeling ($p < 0.001$), irritability ($p < 0.05$), tiredness ($p < 0.001$), mood swings ($p < 0.01$), sleep difficulties ($p < 0.01$), weakness ($p < 0.01$), ability to concentrate ($p < 0.05$) and pain ($p < 0.05$). There was a significant amelioration of depression according to the MFQ-S ($p < 0.05$).

Conclusion: This study showed low levels of vitamin D in 54 depressed adolescents, positive correlation between vitamin D and well-being, and improved symptoms related to depression and vitamin D deficiency after vitamin D supplementation.

INTRODUCTION

Depression is a multifaceted disorder with symptoms such as negative affect, loss of interest, and somatic complaints such as fatigue and pains. In a North American community sample, the prevalence of major depressive disorder in adolescents was estimated to about 4–8% (1). In Sweden, the prevalence is about 2–6% (2). Fombonne in a review concluded that there was an increase in depression in younger cohorts, perhaps indicating socio-environmental changes (3).

In 1979, a study by Bech and Hey found a correlation between levels of vitamin D and asthenia symptoms in depressed adult patients (4). A biological link between vitamin D and mood was originally suggested by Stumpf and Privette, based on findings of vitamin D effects in the rodent brain (5). A high concentration of vitamin D receptors can be found in the amygdala, the thalamus, the hypothalamus, the dorsal raphe nucleus, the dorsal nucleus of the vagus and motor neurons located both cranially and spinally, suggesting effects on sensory pathways, the endocrine-autonomic system and the motor system (6). Thus, symptoms of depression such as fatigue, mood regulation, motor function and pain might be related to effects of vitamin D deficiency. Studies by Landsdowne and Provost, and Vieth have showed that healthy adults experienced better mood and an increase in well-being when they had vitamin D supplementation (7,8). A chart review from Sweden found low

Key notes

- In this case-series, the level of vitamin D in a group of 54 Swedish depressed adolescents was studied, as well as the effects of vitamin D supplementation.
- The results showed a positive correlation at baseline between levels of vitamin D and well-being, and a negative correlation between tiredness and bodily weakness.
- After supplementation, there was an increase in well-being as well as a decrease in depression scores.

vitamin D levels in a mixed diagnosis population at a general psychiatric out-patient clinic (9). Recently, an association between depressive status and decreased serum vitamin D levels in the elderly has been reported (10). Similarly, a study in adolescents showed an association between vitamin D and school absenteeism and arthralgia in children (11). The prevalence of vitamin D deficiency is higher in obese and overweight adolescents than in overweight children (12). A recent review concluded that 'there is some evidence to suggest that vitamin D deficiency or insufficiency may make a contributory role to depression' (13).

Stockholm in Sweden is a town close to northern latitude 60, which is passing areas such as Hudson Bay, and the Kamchatka peninsula. At this latitude, the solar angle is small and there is low UVB availability from October to April. As the major source of vitamin D is a reaction in the skin, mediated by short-wave-length ultraviolet radiation (UVB, 280–320 nm), there is a very low production of vitamin D during this season (14).

At Huddinge BUP Child Psychiatric Clinic, Stockholm, Sweden, the doctors serve in teams with psychologists and social workers. Severely depressed youths with suicidality and somatic complaints are referred to the doctors for evaluation. As part of this evaluation, laboratory testing is often carried out. The serum level of 25OHD has been shown to be the best indicator of vitamin D status of an individual, correlating with the vitamin D stores, and during the years 2007–2011, analysis of serum 25OHD was added to the testing (15). Subjects who were low in 25OHD were supplemented with oral vitamin D_3. Here, we present the resulting case-series of depressed youths. As far as we know, there are no previously published data on depressed adolescents and levels of vitamin D.

This chart review was a clinical quality assurance project. All patients were informed about the testing and the results and treated with vitamin D when there was a deficiency.

METHODS

Fifty-four cases of depressed adolescents (37 girls and 17 boys, range 10–19, mean age 16, SD 1.8) were examined for psychiatric and somatic evaluation. Among them, 19 were considered by the clinicians to suffer from moderate depression and 35 from severe depression.

Criteria for severe depression were suicidal ideation and suicide attempts. Standard treatment was psychotherapy or supportive counselling and in some cases also medication, methylphenidate for comorbid attention-deficit disorder in two cases, the antidepressant fluoxetine in three cases and duloxetine in one case. Body mass index was not recorded, but none of the subjects was described as obese. There were nine subjects of immigrant origin, but none with dark skin.

The months for venous blood collection for serum preparation were January (n = 7), February (n = 10), March (n = 6), April (n = 10), May (n = 1), June (n = 2), July (n = 3), September (n = 3), October (n = 5), November (n = 3) and December (n = 4). As this was a naturalistic study, subjects could choose between laboratory 1 (lab 1) and laboratory 2 (lab 2). Serum levels of 25OHD were analysed in lab 1 by a chemiluminescent assay method from DiaSorin on a LIAISON instrument (DiaSorin S.p.A., Saluggia, Italy) with equimolar measurement of both 25OHD D_2 and D_3, free and dissociated from vitamin D-binding protein (n = 35). In lab 2, the analyses were carried out using a radioimmunoassay method from Immuno Diagnostic Systems Nordic (IDS Nordic a/s, Herlev, Denmark) (n = 19).

Vitamin D_3 (Holistic, Motala, Sweden) was recommended during 3 months (4000 IU daily during 1 month and 2000 IU daily for 2 months) to all subjects with 25OHD levels below 60 nmol/L (n = 48). The supplementation was administered orally as capsules at home, and the participants had to pay for the supplementation themselves.

Self-rating scales

To evaluate the effect of vitamin D supplementation, the WHO-5 well-being scale (WHO-5) and a vitamin D deficiency scale were used. The WHO-5 is a well-being scale aimed at measuring mental status in both somatic and psychiatric disorders, and it has been studied in a group of 97 adolescents and was found to have good psychometric properties and correlation with a depression rating scale (16). Patients were asked to rate how they had felt over the last 2 weeks. Questions include: (i) I have felt cheerful and in good spirits, (ii) I have felt calm and relaxed, (iii) I have felt active and vigorous, (iv) I woke up feeling fresh and rested and (v) My daily life has been filled with things that interest me. The WHO-5 percentage score was calculated, with a score of 100 representing best possible quality of life and 0 representing the worst possible. A score <50 was observed in depressed youths in another study (16). In a group of 1620 teenagers in England and Scotland (17), the WHO-5 means score was 62 (SD 21) (personal communication).

At the end of the case-series, the Mood and Feelings Questionnaire short version (MFQ-S) was introduced. MFQ-S is a widely used questionnaire with good validity and reliability (18).

A vitamin D deficiency scale was developed to highlight aspects that might be associated with both depression and vitamin D status. This scale was developed by author Göran Högberg on the basis of previous clinical findings and the literature on vitamin D deficiency (delivered at request). The participants were asked to rate from 0 to 10 how they felt on nine different items during the last week (Table 1). The three scales were administered at baseline and 4 months later after the recommended period of vitamin D supplementation.

Statistical analysis

To compare basal data between boys and girls and 25OHD levels between the seasons of low and high UVB availability, Student's *t*-test was used. The Mann–Whitney *U*-test was used to analyse differences in the WHO-5 and the vitamin D deficiency scale between boys and girls, and between medicated and nonmedicated subjects. Differences in 25OHD levels before and after vitamin D supplementation were analysed by Student's paired *t*-test.

Table 1 Serum levels of 25OHD, scores in WHO-5 well-being index, MFQ-S and the vitamin D deficiency scale items before, and after, supplementation with vitamin D shown as means ± SD

Instrument	Variable	Before Mean (SD), n	After Mean (SD), n	p
25OHD lab 1	Serum level 25OHD	35 (13) nmol/L n = 35	91 (27) n = 23	<0.001
25OHD lab 2	Serum level 25OHD	50 (15) nmol/L n = 19	90 (21) n = 8	<0.001
WHO-5, range 0–100, the higher the better	Total sum	25 (18) n = 44	43 (25) n = 30	<0.001
MFQ-S, the lower the better	Total sum	14.7 (3.7), n = 11	7.1 (5.3), n = 9	<0.05
Vitamin D deficiency scale 0–10, the lower the better				
	Tired during the day	7.4 (2.5), n = 41	5.2 (3.1), n = 33	<0.001
	Insomnia	5.3 (3.4), n = 41	3.6 (3.6), n = 33	<0.01
	Bodily weakness	6.3 (3), n = 41	4.5 (3.4), n = 33	<0.01
	Aches and pains	5.1 (3.1), n = 41	3.4 (3.2), n = 33	<0.05
	Depressed feeling	6.5 (2.7), n = 41	4.3 (2.9), n = 32	<0.001
	Irritability	6.4 (2.5), n = 41	5.2(3.2), n = 33	<0.05
	Difficulties with mood regulation	6 (3), n = 40	4.6 (3), n = 32	<0.01
	Difficulties to concentrate	6.1 (3), n = 37	4.3 (3), n = 30	<0.05
	Difficulties to think clearly	4.4 (2.8), n = 39	4.2 (2.9), n = 32	ns

Differences in scores in the WHO-5, MFQ-S and the vitamin D deficiency scale before and after vitamin D supplementation were analysed by Wilcoxon signed rank test.

The Spearman rank correlation test was used to investigate correlations between scores in the WHO-5, the vitamin D deficiency scale and the 25OHD levels (in this analysis, only data from laboratory 1 was included as the majority of the samples were analysed in laboratory 1 and the 25OHD levels in the two laboratories differed).

The statistical software used was STATISTIKA™ version 10 (Statsoft Inc., Tulsa, OK, USA).

RESULTS

Plasma 25OHD levels

Mean serum 25OHD levels in the depressed adolescents before and after supplementation are presented in Table 1. Six subjects had an initial serum 25OHD level below 25 nmol/L, indicating severe deficiency. There was no significant difference in 25OHD levels between the seasons of May through October and November through April. Forty-eight subjects were offered vitamin D supplementation. 25OHD levels increased significantly from 41(SD 15) nmol/L before vitamin D supplementation to 91(SD 25) nmol/L after vitamin D supplementation (differences between laboratory 1 and 2 are shown in Table 1). The mean increase was 53 nmol/L (SD 25 nmol/L; range, 12–122). No subject had a serum level of 25OHD <50 nmol/L after supplementation. There were no differences in 25OHD levels between girls and boys before and after vitamin D supplementation, and no differences were found between subjects with severe depression in comparison with moderate depression.

The WHO-5

Basal 25OHD levels correlated positively with well-being at baseline according to the WHO-5 score ($r = 0.42$, $p < 0.05$) (Fig. 1). After supplementation, no correlation was observed.

After vitamin D supplementation, well-being increased significantly ($p < 0.001$) (Table 1, Fig. 2).

No differences between boys and girls or between medicated and nonmedicated subjects were found.

Vitamin D deficiency scale

Basal 25OHD levels correlated negatively with the baseline scores for items of 'tiredness' and 'bodily weakness' ($r = -0.60$, $p < 0.05$ and $r = -0.39$, $p < 0.05$, respectively). There was no correlation between the increase in 25OHD levels and the individual items.

There was a significant improvement in eight of the nine items in the vitamin D deficiency scale, which showed a decrease in depressed feeling ($p < 0.001$), tiredness ($p < 0.001$), irritability ($p < 0.05$) mood swings ($p < 0.01$), sleep difficulties ($p < 0.01$), bodily weakness ($p < 0.01$), ability to concentrate ($p < 0.05$) and pain ($p < 0.05$). No

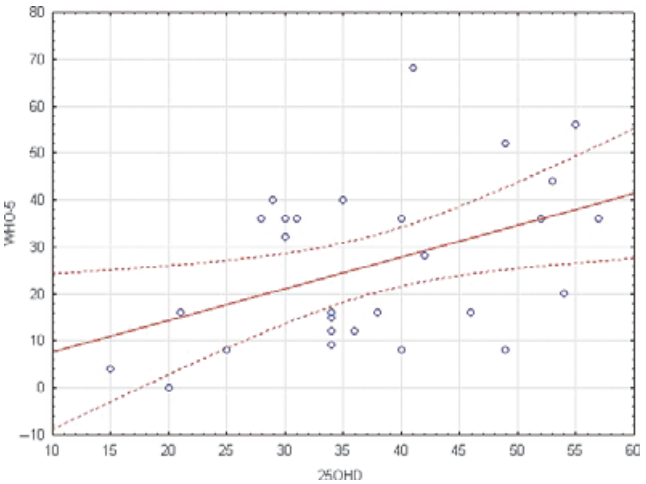

Figure 1 Correlation between 25OHD levels before vitamin D supplementation and the WHO-5 well-being index (n = 28), confidence interval 0.95. Statistical evaluation was performed by the Spearman rank correlation test. R = 0.42, $p < 0.05$.

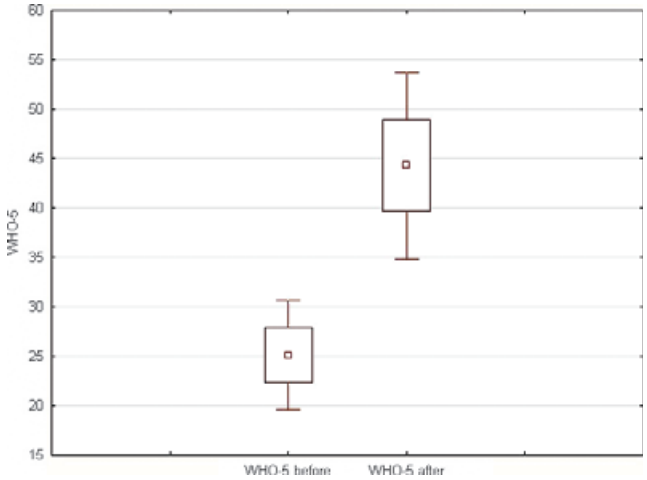

Figure 2 The means, SE and 95% confidence interval in the WHO-5 well-being scale before and after supplementation with vitamin D.

differences between boys and girls were found, and again, no differences were found between medicated and nonmedicated subjects.

The difference between the variables in the vitamin D deficiency scale before and after supplementation is shown in Table 1.

MFQ-S

There was a significant decrease ($p < 0.05$) after supplementation in the scores of MFQ-S from 14.7 - indicating depression - to 7.1 - which is below the threshold of depression.

DISCUSSION

In this study, well-being correlated with serum 25OHD levels and several symptoms that might be related to vitamin D deficiency. In addition, depression decreased after vitamin D supplementation. An interesting finding in this series is the nonsignificant effect of season on the levels of 25OHD. We hypothesize that depressed adolescents might have a sun-avoiding lifestyle, spending a greater amount of time indoors and perhaps in night time spent in front of the computer. Such lifestyle factors may be of importance in the observed increase in depression in younger people (3).

The large range of increase in 25OHD levels post-supplementation might reflect variability in intake. This factor could be controlled in future studies by administering supplementation at the clinic in monthly doses.

The changes in the vitamin D deficiency scale parallel those symptoms related to vitamin D deficiency found by Bech and Hey such as insomnia, irritability, fatigue, aches and pains (4). Mood regulation seems to be a specific issue in depressed adolescents as shown by two studies on the affective experiences of depressed youths (19,20). In these studies, it was found that depressed adolescents, in contrast to controls, had difficulties in letting go of negative emotions and in holding on to positive emotional states. This is of interest in the light of the finding of amelioration of mood regulation after vitamin D supplementation in this study.

The significant improvement in well-being in the WHO-5 also indicates an improvement in depressive symptomatology as this scale has been found to correlate well with the severity of depression in the young (16). The significant amelioration in the MFQ-S also indicates a relation between vitamin D and depression. Another finding of interest is the significant decrease in the item 'difficulties to concentrate' as it might indicate a role of vitamin D in adolescent attention-deficit disorders.

The finding of diverging mean vitamin D levels with different laboratory procedures is in line with the known difficulty to reach exact correspondence between laboratories in vitamin D measurements (21). The importance to use the same laboratory and the same assay method in vitamin D research was underscored by Lai et al. (22).

It has been shown that depressed adolescents may have an abnormal immunological reaction in comparison with healthy controls (23), and signs of a persistent inflammatory reaction have been found in depression (24). The cytokine IL-6 is associated with inflammation and was elevated in depressed adolescents in comparison with controls (25). Interestingly, vitamin D is involved in immunological reactions and has been shown to influence the function of T cells and several cytokines (26,27). For example T cells producing IL-6 are decreased in the presence of vitamin D (28). The change in the vitamin D deficiency scale in areas such as fatigue, pain, weakness and insomnia gives a picture of complaints similar to the malaise experienced during inflammatory states. This observation leads to the suggestion that the immune system might be one of the links between vitamin D deficiency and symptoms of depression.

There are no data on 25OHD status in nondepressed Swedish youth, and an important question is whether low levels of vitamin D might be common in the normal adolescent population. The amelioration of depression by vitamin D supplementation cannot entirely be attributed to the vitamin D supplementation and especially not without a placebo group in a randomized study.

CONCLUSIONS

The study showed that 11% of the subjects were suffering from severe vitamin D deficiency (<25 nmol/L), with risk of impaired bone mineralization. This finding alone raises the question whether routine assessment of vitamin D status should be carried out in depressed adolescents. The significant correlation between levels of 25OHD and well-being as well as the observed improvement in depression and well-being with vitamin D supplementation indicates a relation between vitamin D status and depression. Vitamin D status and depression should be further explored by comparing the vitamin D status between depressed and nondepressed adolescents as well as by randomized controlled supplementation studies.

ACKNOWLEDGEMENT

We would like to express our gratitude to Dr Monica Leu for valuable comments on the text.

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