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Original Research Article

Urinary iodine and serum 25-hydroxyvitamin D are associated with depression in adolescents

Wei Huang, Dehong Gong*, Yongbo Bao
Department of Pediatric Care, Zaozhuang City Hospital, Zaozhuang 277100, China

For correspondence:* ***Email:* *Gongdehongllk@163.com*

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Abstract

Purpose: *To determine whether depressive disorder (DD) in adolescents is associated with the levels of serum 25-hydroxyvitamin D {25(OH)D} and urinary iodine.*
Methods: *A total of 270 adolescent participants from 8 to 16 years old were enrolled in this study (male, n = 125; female, n = 145). Of these, 160 paticipants (male, n = 75; female, n = 85) were diagnosed with DD and 110 paticipants (male, n = 50; female, n = 60) were non-DD. Urinary iodine level, serum 25(OH)D level, and thyroid function were measured and adjusted for sex, age, body mass index, and disease progression. Vitamin D (25(OH)D) < 15 ng/mL was considered as VD deficiency, and iodine <100 μg/L was viewed as iodine deficiency. Mean VD and iodine levels were compared between DD and control groups.*
Results: *DD patients had lower concentrations of 25(OH)D_3 ($p < 0.005$) and urinary iodine ($p < 0.05$) than non-DD control, in both male and female cohorts. However, serum 25(OH)D_2 concentration did not significantly correlate with depressive symptoms.*
Conclusion: *Adolescents with DD have markedly lower serum 25(OH)D concentrations and urinary iodine levels than control patients. This relationship is positively associated with disease progression, suggesting possible nutritional intervention measures for neuroprotection.*

Keywords: *25-Hydroxyvitamin D, Iodine, Adolescence, Depression*

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INTRODUCTION

Depressive disorder (DD) is common and affects 1 – 6 % of adolescents worldwide [1]. The Global Burden of Disease report estimated that the social and economic loss due to DD is as substantial as the burden caused by cardiovascular and cancer diseases [2]. Recent studies have demonstrated that DD is associated with lower vitamin D in adults, but this association has not yet been studied in adolescents [3].

It is well known that 25(OH)D primarily participates in calcium homeostasis[4]. In addition, many studies have demonstrated that 25(OH)D is associated with cancer, diabetes, cardiovascular disease, and obesity [5-8]. Thus, it has been hypothesized that 25(OH)D may participate in maintaining the function of cognition. It reported that high 25(OH)D

concentrations may protect against depression in adults [9]. Interestingly, three randomized controlled trials reported that vitamin D_3 supplements improved depression symptoms in obese adults [10], however, further vitamin D_3 supplement trials had no significant effect on symptom improvement in elderly subjects [11].

Iodine is essential for thyroid hormone synthesis [12]. However, there is currently no clear data regarding the effect of iodine levels in depressive disease [13]. In fact, in response to reserved radioactive iodine therapy, many patients displayed symptoms of hypothyroidism, including fatigue, sleep disturbance, and depression, likely due to iodine imbalance in the body [14].

In the current study, the relationships between serum 25(OH)D concentrations, iodine levels, and depressive symptoms in adolescents were explored. Additionally, the relationships among depression and many factors, such as sex, age, body mass index (BMI), and social status were also investigated to explore the effects of iodine intake and vitamin D levels on DD in the population.

EXPERIMENTAL

Participants

A total of 270 participants were enrolled (125 males and 145 females) from March 2016 to May 2018. All participants were 8 – 16 years old and had a BMI ranging from the 5th to 95th percentiles. DD (75 males and 85 females) was diagnosed by local psychiatrists. Healthy control subjects (50 males and 60 females) were enlisted from outpatient pediatric health care centers affiliated with the Zaozhuang, City Hospital for Children. Adolescents who received medical treatments that could affect thyroid function in the preceding 2 months were excluded. Adolescents with suicidal ideation were also excluded. Informed consent was obtained from all participants. This study was approved by the Ethics Committee of Zaozhuang City Hospital.

Psychological health assessment

Under the supervision of professional investigators, mental health assessments were carried out by self-reported mental health questionnaire. Depressive symptoms included feeling despair and/or sad continuously for more than 2 weeks to a point that interferes with normal study and life. According to the questionnaire results, all participants were grouped into two groups: a “depression” group and a “non-depression” group. Depression was assessed as previously described [15,16].

Data collection

Blood and urine samples were collected as a part of the clinical routine at admission. After consent was given and within an hour of collection, the samples were transferred at 4°C according to approved standard operation procedures to the clinical laboratory of the Zaozhuang City Hospital. The levels of thyroid-stimulating hormone FT4, serum 25(OH)D and urinary iodine were measured using ELISA Kits. Vitamin D < 15 ng/mL was defined as vitamin D deficiency [17] and iodine < 100 µg/L was defined as iodine deficiency. The levels of vitamin D and iodine were compared between control (non-DD) and DD groups.

Statistical analysis

Student’s t-test, analysis of variance (ANOVA) and Pearson's Chi-squared test were performed using SPSS 25.0. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of the subjects

The clinical characteristics of the control and DD subjects are generalized in Table 1. DD patients displayed no difference from healthy control subjects in height, weight, and age. However, females with DD had a higher BMI ($p = 0.04$). None of the males with DD was hypogonadal, and all females with DD had normal menses. There was also no difference observed in the thyroid hormone, FT4, level between the DD and control groups. Differences in smoking and drinking history between DD and control groups were analyzed. Tobacco use was more frequent in females with DD than control subjects ($p = 0.01$). Additionally, there were more male DD patients with smoking and drinking history than female DD patients. Fifty-eight males and 70 females were using selective serotonin reuptake inhibitors (SSRIs), and 24 males and 31 females were using atypical antipsychotics.

Serum 25(OH)D and urinary iodine levels in DD and control groups

The levels of serum 25(OH)D_2, serum 25(OH)D_3, and urinary iodine were evaluated in participants. Serum 25(OH)D_2 concentrations were not closely related to depressive symptoms in adolescents (data not shown).

Table 1: Clinical characteristics of males and females with DD and healthy control participants

Variable	Male		*P*-value	Female		*P*-value
	DD (n=75)	Ctrls (n=50)		DD (n=85)	Ctrls (n=60)	
Age (years)	12.1±2.6	11.6±2.8	0.28	12.0±2.7	12.3±2.8	0.62
Height (cm)	149.4±18.0	154.0±17.5	0.11	129.7±16.3	132.9±19.8	0.28
Weight (kg)	50.2±11.7	52.2±12.0	0.34	37.2±9.3	38.1±10.8	0.57
BMI (kg/m^2)	22.2±1.3	21.6±2.0	0.06	21.9±2.1	21.2±1.5	**0.04***
DD subjects with history of SSRI use	58.7%			70.6%		
DD subjects with history of atypical antipsychotic use	24.0%			31.8%		
History of smoking	17.3%	10%		5.8%	0%	**0.01***
History of alcohol	25.3%	16.6%		0%	0%	
FT4 (pmol/L)	22.0±4.5	22.6±4.3	0.08	22.4±3.0	23.6±3.4	0.38

Data are presented as mean ± SD; * t-test and Pearson's Chi-square were used to analyze differences between groups; Ctrl = control

The mean concentrations of total serum 25(OH)D [25(OH)D_2 + 25(OH)D_3] in DD and control participants were 17.4 ± 4.3 and 22.9 ± 5.0 ng/mL, respectively. In addition, the mean concentrations of urinary iodine in DD and control participants were 175.7 ± 66.5 and 250.8 ± 88.6 ng/mL, respectively. The results indicate that both serum 25(OH)D and urinary iodine levels were significantly lower in DD adolescents than in the control subjects, suggesting a close relationship between DD 25(OH)D, and iodine levels *in vivo*.

Age and sex index

Serum 25(OH)D concentrations varied significantly with sex and age (Table 2). For children 8 to 12 years old, 3.2 % had 25(OH)D levels < 12 ng/mL, and 45.2 % had 25(OH)D levels < 20 ng/mL. In contrast, these levels were 10.4 and 54.9 % for teenagers 8 - 16 years old, respectively. For children 8 to 11 years old, 2.4 % had iodine levels < 100 µg/L, and 76.2 % had iodine levels < 300 µg/L. For teenagers 8 to 16 years old, 13.9 % had iodine levels < 100 µg/L, and 80.6 % had iodine levels < 300 µg/L. Regardless of gender, the mean levels of 25(OH)D and iodine were lower for teenagers than children (Figure 1A). Otherwise, > 19 % of adolescents had urinary iodine levels < 300 µg/L, and this value was lower in DD patients compared with normal control participants. The mean value of iodine among females 12 to 16 years old was 179.1 µg/L, which was lower than that of males (184.2 µg/L) of the same age (Figure 1B).

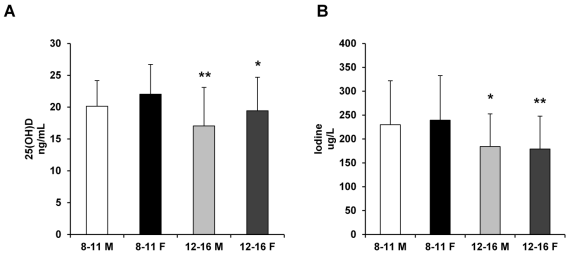

Figure 1: Serum 25(OH)D and urinary iodine values by age and sex. (A) The level of serum 25(OH)D was measured. (B) The level of urinary iodine was measured. *P*-values indicate significant differences between 8–11 years and 12–16 years of the same gender. t-test analysis was used for the comparison. *p < 0.05, **p < 0.01. □: 8–11 year-old males; ■: 8–11 year-old females; ▨: 12–16 year-old males; ▩: 12–16 year-old females

Table 2: Serum 25(OH)D and urinary iodine values of males and females

Biomarker		Males 8–11y		Males 12–16y		*P*	Females 8–11y		Females 12–16y		*P*
25(OH)D	*<12ng/mL*	11.1±0.7	3.2%	10.5±1.1	11.1%	**0.027***	11.3±0.2	3.1%	10.5±1.3	43.8%	**0.000***
	<20ng/mL	17.5±1.7	46.8 %	15.7±1.9	65.1%	**0.000***	17.1±2.3	9.9%	16.9±2.2	46.9%	**0.000***
Iodine	*<100µg/L*	99.1±0.5	3.2%	94.8±5.2	14.0%	**0.007***	97.5±1.0	1.2%	85.3±12.0	13.6%	**0.000***
	<300µg/L	193.5±45.8	74.2 %	180.5±31.8	76.2%	0.3	203.7±55.4	78.1 %	189.7±57.6	83.9%	**0.001***

Data are presented as mean ± SD; *p*-values represent comparison between 8 - and 12 - 16 year old cohort; * t-test and Pearson's chi-square were used to analyze differences between groups

Association between serum 25(OH)D, urinary iodine, and depressive symptoms

The mean value of serum 25(OH)D in teenagers with DD was 15.8 ± 3.7 ng/mL, whereas that of teenagers without DD was 22.4 ± 4.4 ng/mL. The mean levels of serum 25(OH)D in children with DD was 19.4 ± 4.2 ng/mL, whereas that of the controls was 23.3± 5.6 ng/mL. Thus, serum 25(OH)D levels of both teenagers and children with DD were markedly lower than those of age-matched control participants without DD. Moreover, serum 25(OH)D levels of teenagers were significantly lower than those of children (8-11-year-olds) with DD, but this difference was not observed among healthy controls (Table 3).

The mean serum 25(OH)D levels and urinary iodine levels of adolescents with DD were reduced when compared with the control participants in each social class. However, no statistically significant differences were found between social classes in DD or control subjects. High concentrations of urinary iodine were closely related to lower risk of depression at ages 12–16 and at ages 8–11. Table 3 also shows that the urinary iodine concentration in teenagers with DD was 149.5 ± 49.9 µg/L whereas that of teenagers without DD was 231.4 ± 63.6 µg/L. The mean urinary iodine level of children with DD was 207.7 ± 70.5 µg/L whereas that of the control subjects was 270.6 ± 105.9 µg/L. There was a statistical association of iodine values with depressive symptoms in adolescents of every social class.

Analysis of the correlation between urinary iodine and vitamin D in DD

Next, the prevalence of depression according to serum 25(OH)D levels and urinary iodine concentrations was examined (Table 4). In the 25(OH)D deficient group, the prevalence of depression was higher in iodine deficiency (5.6 %) than with iodine adequacy (0.6 %). In both the 25(OH)D sufficient and insufficient groups, there was no significant association between the prevalence of depression and iodine deficiency. The same analysis was conducted in the control group. Among the control participants, there was also a significant association between 25(OH)D and iodine intake in the 25(OH)D deficient group.

DISCUSSION

Although the association between dietary patterns and depression risk has been proposed recently [18-20], only a few investigations have analyzed the association between micronutrient status and incidence of chronic diseases, such as DD.

Table 3: Relationships among age, social class, serum 25(OH)D, and urinary iodine, and depressive symptoms

Variable	DD	Ctrlsnon-DD	*P*-value	DD	Ctrlsnon-DD	*P*-value
	Serum 25(OH)D levels			***Urinary iodine levels***		
Age group						
8–11 years	19.4±4.2	23.3±5.6	***0.000****	207.7±70.5	270.6±105.9	**0.000***
12–16 years	15.8±3.7	22.4±4.4	***0.000****	149.5±49.9	231.4±63.6	**0.000***
P-value	***0.000****	0.34		***0.000****	***0.02****	
Social class						
Upper social class	17.8±2.5	21.5±3.3	***0.000****	187.5±76.4	258.5±99.4	**0.000***
Middle social class	16.9±3.2	21.7±4.2	***0.000****	176.5±84.7	248.9±101.3	***0.000****
Lower social class	16.3±4.1	22.5±5.2	***0.000****	174.3±88.4	244.6±78.4	***0.000****
P-value	0.56	0.73		0.94	0.84	

Data are presented as mean ± SD; *T-test was used to analyze percentage differences between groups

Table 4: Prevalence of DD stratified by serum 25(OH)D and urinary iodine levels

	Urinary iodine group			
25(OH)D group	***Deficiency***	***Adequate***	***Excessive***	***P*-value**
DD				
Deficiency	9 (5.6%)	7 (4.4%)	1 (0.6%)	**0.000***
Insufficiency	11 (6.9%)	87 (54.4%)	5 (3.1%)	
Sufficiency	4 (2.5%)	34 (21.3%)	2 (1.3%)	
Ctrls				
Deficiency	1 (0.9%)	1 (0.9%)	1 (0.9%)	**0.017***
Insufficiency	0	23 (20.9%)	9 (8.2%)	
Sufficiency	2 (1.8%)	55 (50.0%)	18 (16.4%)	

Data are presented as mean ± SD; *p*-values are based on comparison between DD cohort and non-DD cohort; * T-test and Pearson's Chi-square were used to analyze differences between groups

For example, low serum levels of folate, 25(OH)D, or zinc have been reported to be related to depressive symptoms in clinical studies [21-23]. These findings suggest that micronutrient deficiencies are directly associated with increased risk of developing DD. In the present study, the possible association between the levels of serum 25(OH)D or urinary iodine and depression was explored in Chinese adolescents. A previous finding showed that adolescents with psychotic manifestations had lower serum 25(OH)D levels [24]. Another clinical study also found that participants with major depression or schizophrenia had lower $25(OH)D_3$ levels [25]. Moreover, a study in patients with mild Alzheimer's disease demonstrated that subjects with lower 25(OH)D levels (< 20.0 ng/mL) were more susceptible to mood disorders [26]. In our current study of adolescents from 8 to 16 \-year old, lower concentration of 25(OH)D was found to be associated with higher risk of depression. This finding was independent of many potential confounders as well as the concentration of $25(OH)D_2$, which was not closely associated with depression. This was not surprising as previous findings have identified $25(OH)D_3$ as the main contributor to total serum 25(OH)D.

Further, the influence of 25(OH)D in the risk of developing depressive symptoms was greater in teenagers (12–16 years old) with total 25(OH)D deficiency than in children (8 – 11 years old). The association of 25(OH)D with DD symptoms was stronger in teenagers than children. It is possible that adolescents with low concentrations of 25(OH)D develop depressive symptoms as a result of chronically insufficient concentrations of 25(OH)D. However, the biological pathways linking $25(OH)D_3$ to DD require further investigation.

Urinary iodine is a well-known indicator of iodine intake. The WHO categorized iodine nutritional status as deficiency or excessive iodine intake with cut off levels of 100 and 300 µg/L, respectively. Thus, participants in this study were divided into three groups: excessive (≥ 300 µg/L), adequate (100 – 300 µg/L), and deficient (< 100 µg/L) iodine intake. Iodine is an essential element for the production of thyroid hormones, but the present study shows that the prevalence of DD was higher in the adequate iodine intake group than the excessive group. The stronger association of urinary iodine with DD is an interesting finding. However, the differences could also be affected by possible confounding factors, $25(OH)D_3$ or outdoor physical activity, which could influence $25(OH)D_3$ production. Otherwise, in the 25(OH)D deficient groups, the link between the risk of depression and iodine content was obvious in both DD and control subjects.

In 25(OH)D sufficient and insufficient groups, there was no obvious trend between iodine concentrations and the prevalence of depression. This suggests that serum levels of 25(OH)D ≥ 20 ng/mL might prevent the development of DD. However, it is also possible that this phenomenon may be a result of the low number of 25(OH)D deficient subjects, or the relationship between DD and iodine intake is statistically insignificant in a larger population. Given the worldwide iodine abuse, it is important to determine the elements associated with DD in vitamin D-replete populations. The present work suggests that vitamin D sufficiency may prevent the progression and development of DD, regardless of iodine intake. As the exact association between 25(OH)D and iodine remains unclear, our results provide evidence that iodine concentration is associated with 25(OH)D levels in healthy control patients.

This study had several limitations. This cross-sectional study did not clarify the mechanism underlying the impact of serum 25(OH)D and urinary iodine levels on DD. Secondly, the depressive symptoms were diagnosed by self-reported questionnaires to screen for depression, which still remains uncertain. Finally, the volume of dietary vitamin D intake may be possibly affected by the inclusion of subjects with gastrointestinal disorders who might have relatively low serum levels of 25(OH)D due to poor absorption. Despite these limitations, the present study is important in demonstrating that serum 25(OH)D and urinary iodine are both related to depressive symptoms in adolescents at 8 – 16 years of age.

CONCLUSION

Adolescents with DD have significantly lower levels of serum 25(OH)D and urinary iodine than healthy control patients. Additionally, depression is associated with age, gender, BMI, and smoking.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. Dehong Gong designed all the experiments and revised the paper. Yongbo Bao performed the experiments, while Wei Huang wrote the paper.

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