Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Lower vitamin D levels are associated with depression in patients with gout

This article was published in the following Dove Medical Press journal:
Neuropsychiatric Disease and Treatment

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Background: Depression is commonly observed among patients with gout. Low levels of vitamin D have been associated with depression in non-gout subjects. We examined the association of vitamin D levels with depression in patients with gout.

Methods: We conducted a cross-sectional study of 186 gout patients at the Endocrinology Department of First Affiliated Hospital of Jiaxing University. Levels of serum 25-hydroxyvitamin D (25(OH)D) were determined using a competitive protein-binding assay. The 17-item Hamilton Depression Scale was used for screening for depressive symptoms. Diagnosis of depression in gout patients was made in accordance with *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* criteria for depression. Multivariate analysis was performed using logistic regression models.

Results: Thirty-two gout patients (17.2%) were diagnosed as having depression. Patients with depression showed significantly lower 25(OH)D levels as compared to patients without depression (46.4±19.0 vs 57.0±17.3 nmol/L, $P<0.001$). Significant differences in 25(OH)D quartiles of gout patients were observed between the patients with depression and the patients without depression ($P=0.003$). In multivariate analyses, serum 25(OH)D levels (≤40.0 nmol/L) were independently associated with depression in patients with gout (OR 3.833, 95% CI 1.406–10.453, $P=0.009$).

Conclusion: Our study demonstrates an important association between serum vitamin D levels and depression in patients with gout.

Keywords: depression, vitamin, gout

Introduction

Gout is an inflammatory arthritis related to hyperuricemia that is triggered by the crystallization of uric acid within the joints. Gout is a common rheumatic disease worldwide, with an overall prevalence of ~1.14% among Chinese adult population.[1] Depression is frequently observed among patients with gout, with its prevalence ranging from 13% to 20%.[2–5] The presence of depression has been associated with poorer medication adherence, reduced quality of life, and poorer management outcomes.[6,7] Therefore, it is important to identify risk factors for the presence of depression in patients with gout.

Receptors of vitamin D have been detected in areas of the human brain involved in depression.[8] An association between lower vitamin D levels and depression has been found in both healthy and clinical populations.[9–12] Moreover, numerous randomized controlled trials have shown a positive effect of vitamin D supplementation on depression.[13,14]

A previous study has shown low levels of serum vitamin D among patients with gout and a significant association between low vitamin D levels and gout activity.[15] To date, however, no study has investigated the possible association between vitamin D levels

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Dovepress
http://dx.doi.org/10.2147/NDT.S193114

and depression in patients with gout. Given the involvement of vitamin D in depression in non-gout patients and the well-documented high prevalence of low vitamin D levels in gout patients, we conducted a cross-sectional study of 186 gout patients to determine the possible association of serum vitamin D levels with depression in gout patients.

Methods

Participants

Patients with gout were consecutively recruited from the Endocrinology Department of the First Affiliated Hospital of Jiaxing University between July 10, 2013 and May 18, 2017. Gout patients aged ≥18 years and fulfilled the 1977 American College of Rheumatology preliminary criteria for the diagnostic of gout were included in this study.[16] The exclusion criteria were: 1) patients with communication or cognitive disorders; 2) patients with pre-gout depression (clinical diagnosis or previous treatment) or other psychiatric disorders; 3) patients taking vitamin D replacement therapy. Meanwhile, 200 healthy volunteers without gout, vitamin D replacement therapy, or a history of psychiatric disorders including clinical diagnosis and previous treatment were recruited from a health survey. Written informed consents were obtained from all subjects or their relatives if the patients were illiterate. The study was approved by the Ethics Committee of the First Affiliated Hospital of Jiaxing University and was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical variables

Demographic and clinical variables were obtained from participant report and electronic medical records. Demographic included age, sex, body mass index (BMI), and frequency of alcohol consumption. BMI was calculated as weight (kg)/squared height (m^2). Comorbidities included hypertension, hyperlipidemia, diabetes mellitus, stroke, coronary artery disease, and kidney failure. Gout-specific characteristics included: whether gout had ever been experienced in multiple joint at the same time, frequency of gout attacks in last 12 months, gout duration, and current medication use. A fasting morning venous blood sample was obtained from each participant. Levels of serum 25-hydroxyvitamin D (25(OH)D) were determined using a competitive protein-binding assay (Hoffman-La Roche Ltd., Basel, Switzerland). The inter-assay variation coefficient for 25(OH)D measurement was 8.5%. Serum 25(OH)D levels in gout patients were divided into four quartiles (≤41.0, 41.1–55.0, 55.1–66.0, and ≥66.1 nmol/L), as the raw data of 25(OH)D were skewed.

Assessment of depression

All gout patients were screened for depressive symptoms using 17-item Hamilton Depression Scale (HAMD-17). Patients with a HAMD-17 score of ≥7 were given the Chinese version of the Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, for diagnosis of depression. These evaluations were administered by the same experienced psychologist who was blind to the laboratory results of gout patients, including serum levels of vitamin D.

Statistical analyses

Data were presented as number (percentage) for categorical variables, mean ± SD for normally distributed variables, and medians (25th, 75th percentiles) for non-normally distributed variables. Comparisons between the groups were conducted using the chi-squared test, Fisher's exact test, Student's *t*-test, and Mann–Whitney *U* test, as appropriate. Binary logistic regression including age, sex, and the factors with $P<0.05$ in the univariate analysis was performed to examine significant risk factors for depression in patients with gout. The abnormally distributed parameters were log-transformed for satisfying the log-linearity assumption. The results were presented as ORs with corresponding 95% CIs. All statistical analyses were performed by using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Significance level was defined as *P*-value <0.05.

Results

Baseline characteristics of the study samples

Of 205 patients with gout, 19 were excluded from this analysis: 3 with a history of depression, 2 with a history of dementia, 4 taking vitamin D replacement therapy, and 10 who refused to participate in this study. There were no significant differences in age and sex between our study cohort (n=186) and those excluded. Of 186 participants, 151 were male (81.2%) and their mean (SD) age was 61.9 (10.9) years. The patients in this study did not differ from the controls in terms of age and sex.

Univariate associations

Of the 186 patients who formed the study sample, 32 (17.2%, 26 men and 6 women) were diagnosed with depression. Eighteen depressed patients (56%) agreed to have an antidepressant medication with selective serotonin reuptake inhibitors. Serum levels of 25(OH)D were markedly lower in patients with depression than in healthy controls (55.2±18.0

vs 65.1±19.7 nmol/L, $P<0.001$). Patients with depression showed significantly lower 25(OH)D levels as compared to patients without depression (46.4±19.0 vs 57.0±17.3 nmol/L, $P<0.001$). No correlation was detected between 25(OH)D levels and age, gender, calcium, phosphorus, albumin as well as with hemoglobin (all $P>0.05$). In addition, patients with depression had more gout attacks in multiple joint ($P<0.001$) and higher frequency of gout attacks ($P<0.001$). Significant differences in 25(OH)D quartiles of gout patients were observed between the patients with depression and the patients without depression ($P=0.003$) (Table 1).

Multivariate regressions

With all gout patients taken as a whole, depression occurrence taken as a dependent variable, and quartile 2 and quartile 3 taken as the references used for serum 25(OH)D levels in the logistic analysis, 25(OH)D levels (≤40.0 nmol/L) were independently associated with depression in patients with gout (OR 3.833, 95% CI 1.406–10.453, $P=0.009$). In addition, frequent gout attacks and attacks in multiple joints were significantly associated with depression in gout patients (OR 6.136, 95% CI 1.737–21.674, $P=0.005$; OR 4.454, 95% CI 1.468–13.512, $P=0.008$, respectively) (Table 2).

Table 1 Patient characteristics stratified by depression

Characteristics	Patients with depression (n=32)	Patients without depression (n=154)	Healthy volunteers (n=200)	*P*-value[a]
Age, mean ± SD, years	61.5±10.1	62.0±11.1	62.3±8.2	0.820
Male, n (%)	26 (81.3)	125 (81.2)	116 (58.0)	0.991
BMI, kg/m^2				0.319
<25.0	14 (43.8)	43 (27.9)	59 (29.5)	
25.0–29.9	9 (28.1)	58 (37.7)	76 (38.0)	
30.0–34.9	5 (15.6)	36 (23.4)	45 (22.5)	
≥35.0	4 (12.5)	17 (11.0)	20 (10.0)	
Alcohol consumption, n (%)				0.557
Daily	8 (25.0)	43 (28.3)		
3–4 times per week	9 (28.1)	30 (19.7)		
1–2 times per week	7 (21.9)	32 (21.1)		
Occasionally	3 (9.4)	30 (19.7)		
Never	5 (15.6)	17 (11.2)		
Comorbidity, n (%)				
Hypertension	21 (65.6)	88 (57.1)		0.375
Diabetes mellitus	7 (21.9)	21 (13.5)		0.223
Coronary heart disease	4 (12.5)	14 (8.8)		0.511
Hyperlipidemia	15 (46.9)	60 (39.0)		0.406
Stroke	2 (6.3)	7 (4.5)		0.654
Kidney failure	3 (9.4)	7 (4.5)		0.380
Gout characteristics				
Gout duration, median (IQR), years	6 (4–11)	6 (3–8)		0.178
Frequency of gout attacks				<0.001
0	6 (18.8)	53 (34.4)		0.083
1–2	9 (28.1)	82 (53.2)		0.010
≥3	17 (53.1)	19 (12.3)		<0.001
Gout attacks in multiple joint	25 (78.1)	46 (29.9)		<0.001
Current medication use, n (%)				
Allopurinol	17 (53.1)	92 (57.9)		0.489
NSAID	12 (37.5)	44 (28.6)		0.316
Corticosteroids	3 (9.4)	11 (7.1)		0.712
25(OH)D, n (%)				0.003
Quartile 1	14 (43.8)	28 (18.2)		0.002
Quartile 2	9 (28.1)	31 (20.1)		0.317
Quartile 3	4 (12.5)	39 (25.3)		0.117
Quartile 4	5 (15.6)	56 (36.4)		0.023
25(OH)D, mean ± SD, nmol/L	46.4±19.0	57.0±17.3	65.1±19.7	0.002

Notes: Data are expressed as number (percentage) or mean ± SD or medians (IQR). [a]Compared between the patients with depression and the patients without depression.
Abbreviations: BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

Table 2 Characteristics associated with depression in gout patients[a]

Variables	OR (95% CI)	*P*-value
25(OH)D[b]	3.833 (1.406–10.453)	0.009
Gout attacks in multiple joint	4.454 (1.468–13.512)	0.008
Frequent gout attacks (≥3)	6.136 (1.737–21.674)	0.005
Age	0.986 (0.945–1.029)	0.520
Sex	1.011 (0.322–3.176)	0.985

Note: [a]Includes age, sex, and the variables which were significant ($P<0.05$) in the multivariable model; [b]quartile 1.
Abbreviation: 25(OH)D, 25-hydroxyvitamin D.

Discussion

To the best of our knowledge, this is the first study exploring the possible association between serum vitamin D levels and depression among gout patients. Our results suggest that serum level of vitamin D was significantly associated with depression in patients with gout, which is similar to the findings of previous studies in elderly adults and patients with chronic spinal cord injury.[10,11] Our findings might have important implications in providing novel therapeutic target for depression in patients with gout.

In the present study, 17.2% of gout patients were diagnosed as having depression, which is consistent with the results of earlier studies.[2] Currently, despite the available literature, it remains difficult to determine the actual prevalence of depression in gout patients, possibly due to the differences in study designs, the source of patient recruitment, methods used to diagnose depression, and race/ethnicity. In addition, our results demonstrated that frequent gout attacks and attacks in multiple joints were risk factors for depression in gout patients, which agrees with the findings of previous studies.[5]

Interestingly, we found that serum vitamin D levels were independently associated with depression in gout patients. As mentioned earlier, numerous studies have demonstrated an important association of low vitamin D levels and depression in non-gout subjects. The exact mechanisms by which vitamin D could affect depression are unclear. Vitamin D receptors and vitamin D activating enzyme 1a-hydroxylase are broadly present in specific regions of the human brain, some of which have been involved in the pathophysiology of depression, including the cingulate cortex, hippocampus, hypothalamus, and substantia nigra.[8] Vitamin D response elements have been detected in the promoter regions of serotonin genes.[17] Another possible explanation is the effect of vitamin D on inflammatory response. Vitamin D plays a vital role in modulating the secretion of inflammatory cytokines such as IL-6 and IL-1β.[18,19] Gout is considered to be a chronic inflammatory disease, characterized by elevated inflammatory factors such as IL-6 and IL-1β.[20] It has been hypothesized that depression and gout may share common pathophysiological mechanisms including inflammatory response and immune activation.[20–22] Vitamin D may modulate the association between depression and inflammatory response through its effect on the immune system. Hence, these abovementioned results suggest that vitamin D might play a key role in depression in gout patients.

Limitations

There are several limitations in this study. First, the seasonal variation of vitamin D levels makes it preferable to perform the measurements on the same day. Second, subjects in our sample were recruited from only one clinic, which limited the generalization of the findings. Third, due to lack of data of uric acid levels, we could not analyze the possible association between uric acid levels and depression in gout patients. Finally, the small sample size may reduce the statistical power of the present study.

Conclusion

In summary, despite of these limitations mentioned above, our study demonstrates an important association between vitamin D levels and depression in patients with gout. Further randomized controlled trials are critical in examining whether the supplement of vitamin D holds promise for the treatment of depression in gout patients.

Acknowledgment

The authors express their gratitude to all subjects who participated in the current study.

Disclosure

The authors report no conflicts of interest in this work.

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