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Abbreviations:
25(OH)D: 25-hydroxyvitamin D; PSQI: Pittsburgh Sleep Quality Index; GAD-7, Anxiety Disorder Scale-7; PHQ-9, Patient Health Questionnaire-9; IQR: interquartile range.
Abstract

Background: The association between low 25-hydroxyvitamin D [25(OH)D] and sleep disorder has been reported. We investigated whether serum concentrations of 25(OH)D are altered in chronic insomnia patients. The relationship between serum concentrations of 25(OH)D and the treatment outcome in patients at 2 months was also investigated.

Methods: In total, 181 chronic insomnia patients were consecutively recruited. All patients received pharmacotherapy for the treatment of chronic insomnia. Serum 25(OH)D concentrations were quantified by a competitive electrochemiluminescence protein binding assay. Treatment outcomes were defined as “response” versus “non-response”, according to the change of the Pittsburgh Sleep Quality Index (PSQI). We also recruited 100 healthy subjects as a control group.

Results: Fifty-four out of 181 (29.8%) patients met the criteria for non-response. Chronic insomnia patients had significantly lower 25(OH)D concentrations compared with healthy controls (23.01 ± 9.18 vs 27.17 ± 6.41 ng/ml, P < 0.001). Non-response patients also had significantly lower 25(OH)D concentrations than those with response. Vitamin D deficiency (25(OH)D concentrations < 20 ng/ml) was independently associated with a higher probability of treatment non-response at 2 months (odds ratio 11.636, 95% confidence interval 3.966-34.142, P < 0.001).

Conclusions: Measurement of serum 25(OH)D concentrations are probably useful for judging treatment outcomes of pharmacotherapy in chronic insomnia patients.

Keywords: Chronic insomnia; Vitamin D; Outcome
1. Introduction

Chronic insomnia is among the most prevalent public health problem. Estimates suggest that approximately 10% of adults in Western countries suffer from chronic insomnia [1], similarly, the prevalence of chronic insomnia in China is 9.2% [2]. Previous studies have shown that chronic insomnia is a risk factor for the presence and development of cardiovascular and psychiatric disorders [3-5], thus contributing to substantial direct and indirect health-care costs worldwide. In spite of the well-documented effectiveness of cognitive behavioral therapy for insomnia (CBTI), pharmacotherapy remains the first-line treatment for insomniacs seeking medical care in outpatient care settings [6], partly due to the heavy workload of physicians and the lack of CBTI practitioners. Therefore, determining which type of chronic insomnia patients may or may not benefit from drug-based treatments is of crucial clinical significance in order to achieve optimal treatment response and reduce the health-care burden of insomnia.

Vitamin D is unique among hormones which can either be synthesized in skin by ultraviolet radiation or derived from diet. Among the many forms of vitamin D, 25-hydroxyvitamin D (25(OH)D) is commonly used to determine functional vitamin D status. Serum 25(OH)D concentration is regulated by multiple feedback loops, including parathyroid hormone (PTH) and by serum phosphorus concentrations[7]. Factors such as lack of sunlight exposure, obesity, lifestyle, habits, skin color, pregnancy, as well as liver and renal diseases also affect the concentrations of serum 25(OH)D[8]. Previous studies have shown that low serum 25(OH)D concentrations were associated with cardiovascular diseases[9], mental illness[10], cognitive decline[11] and sleep disorders[12].
In a study, McCarty et al. found that patients who had vitamin D deficiency reported more daytime sleepiness [13]. Massa et al. observed that low serum 25(OH)D concentrations were associated with insufficient sleep duration and low sleep efficiency in American elderly community-dwelling men [14]. Bozkurt et al. found a significant relation between more severe obstructive sleep apnea (OSA) indices and lower serum 25(OH)D concentrations [15]. Majid et al. reported that applied vitamin D supplements could improve sleep quality and extend sleep duration in people with sleep disorders [16]. These studies have suggested the possible link between sleep and vitamin D. However, the association between vitamin D and chronic insomnia remains unclear.

2. Materials and methods

2.1. Participants

This study was performed at First Affiliated Hospital of Wenzhou Medical University between November 2015 and April 2017. Our hospital’s Medical Ethics Committee approved this study protocol and all participants signed the informed consent forms. Patients with chronic insomnia were admitted to the outpatient neurology clinic of our hospital. The diagnosis of chronic insomnia was made according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) [17] by an experienced neurologist via structured clinical interviews. The inclusion criteria were as follows: (1) complaints of difficulty falling or staying asleep, or waking up too early for at least 3 months; (2) significant distress or daytime impairment caused by sleep disturbance; (3) being 18 years or older; and (4) being a first-time patient in our clinic. The exclusion criteria were as follows:
(1) suffering major depression or other mental illness, including alcohol or substance abuse;
(2) presence of an untreated sleep disorder other than chronic insomnia; (3) shift work or
abnormal sleep schedules; (4) pregnancy; (5) having a history of osteoporosis, anemia,
serious chronic diseases (cardiovascular diseases, renal impairment) or neurological
degenerative disease; and (6) taking vitamin D supplementation.

Control subjects with normal sleep were recruited from healthy patients of the First
Affiliated Hospital of Wenzhou Medical University during routine health examinations.
Healthy individuals had no self-reported personal history of psychiatric or physical disorders.
The healthy controls had an age and gender distribution similar to the chronic insomnia
patients, and they reported having normal and satisfactory sleep for at least 1 y.

2.2. Clinical variables

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality of chronic
insomniac participants at baseline and 2 months. The total score of PSQI is 21 points. Higher
scores indicate worse sleep quality. Depressive symptoms were measured by the Patient
Health Questionnaire-9 (PHQ-9) at baseline. Anxious symptoms were measured by the
Generalized Anxiety Disorder Scale-7 (GAD-7) at baseline. Measurements were
implemented by trained researchers blind to all variables of the participants. Regular physical
activity was defined as ≥ 3 times/week with ≥ 30 minutes/time of walking, running, or other
forms of physical activities. Chronic insomnia patients who had used any hypnotic drugs in
the past month were categorized as having received hypnotic drugs.
2.3. Pharmacotherapy

Every patient was treated, as appropriate, with symptom-focused pharmacotherapy at baseline, including zolpidem for delayed sleep latency, zopiclone for frequent episodes of wakefulness, clonazepam for early morning awakening and daytime anxiety, and sedating antidepressants as necessary [18]. We chose benzodiazepines or benzodiazepine receptor agonist drugs based on symptom patterns, past treatment responses, side effects and other factors. The drug treatments were administered according to Clinical Guideline for the Diagnostic and Treatment of Chronic Insomnia in Chinese Adults. The drug doses varied among the insomnia patients. All patients were given an individualized treatment plan. Patients were encouraged to use hypnotic drugs 3-5 nights/week, but could also choose to use hypnotic drugs more frequently. Patients met every two weeks for an outpatient visit with a neurologist for medication management.

2.4. Treatment outcome

In the present study, the treatment effect of pharmacotherapy in chronic insomnia was categorized as 2 binary treatment outcomes: “response” versus “non-response”. As reported in the previous insomnia treatment studies [19,20], patients whose PSQI scores decreased ≥3 with or without a final PSQI score < 5 were categorized as “response”. The “non-response” category consisted of those whose PSQI scores decreased < 3.

2.5. Vitamin D measurements

Blood samples were obtained within 24 hours after visit. Serum 25(OH)D was used to
assess vitamin D status for all participants. The concentrations of serum 25(OH)D were quantified by a competitive electrochemiluminescence protein binding assay (Cobas e602.Roche Diagnostics, Germany) in our hospital’s biochemistry department. The intraassay CV was 7%–10%. A serum concentration of 25(OH)D < 20 ng/ml is considered vitamin D deficiency.

2.6. Statistical analysis

Categorical variables were compared using the $\chi^2$ test, while the Student’s $t$-tests, Fisher’s exact test, one-way analysis of variance (ANOVA) and the Mann–Whitney U test were used for the continuous variables, as appropriate. When there was a meaningful ANOVA, the post hoc Tukey test followed. Bonferroni corrections were used to adjust for multiple testing. Furthermore, we used binary logistic regression to evaluate the forecast value of vitamin D deficiency and other clinical variables on non-response. The results were expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed in SPSS software vers21.0. Findings with $P < 0.05$ (2-tailed) were regarded as statistically difference.

3. Results

3.1 Baseline Characteristics of Study Samples

A total of 221 chronic insomnia patients met the study inclusion criteria. Of these 221 patients, 181 completed a follow-up, while 40 (18.1%) were lost to follow-up at 2 months. No significant difference was observed between the 2 groups in age ($43.16 \pm 10.16$ vs $45.95 \pm$
9.85, \( P = 0.133 \)), gender (M/F) (52/129 vs 15/25, \( P = 0.257 \)), PSQI scores (15.18 ± 2.66 vs 14.95 ± 2.64, \( P = 0.625 \)) and serum 25(OH)D concentrations (23.01 ± 9.18 vs 21.62 ± 6.94 ng/ml, \( P = 0.369 \)). Of the 181 chronic insomnia patients, 54 (29.8%) met the criteria for non-response, and 127 met the criteria for response. The baseline characteristics of response, non-response and healthy control subjects are presented in Table 1.

3.2 Main Findings

Serum 25(OH)D concentrations in 181 chronic insomnia patients were significantly lower than those of healthy controls (23.01 ± 9.18 vs 27.17 ± 6.41 ng/ml, \( P < 0.001 \)). Of the 181 chronic insomnia patients, 82 (45.3%) met the criteria for having received hypnotic drugs. No significant difference was found between chronic insomnia patients with or without hypnotic drugs in serum 25(OH)D concentrations (24.18 ± 9.92 vs 22.04 ± 8.44 ng/ml, \( P = 0.119 \)).

There is a significant intergroup difference in 25(OH)D concentrations between response, non-response and healthy controls groups (\( F =15.12, \ P < 0.001 \)). Non-response patients had significantly lower 25(OH)D concentrations than response patients and the healthy controls (19.63 ± 7.17 vs 24.44 ± 9.58 ng/ml, \( P = 0.001 \); 19.63 ± 7.17 vs 27.17 ± 6.41, \( P < 0.001 \), respectively). Response patients also had lower 25(OH)D concentrations compared with healthy controls. Patients with non-response had lower PSQI, PHQ-9 and GAD-7 scores at baseline than response patients. In addition, patients with non-response had higher PSQI scores at 2 months than patients with response (13.70 ± 2.52 vs 9.72 ± 2.83, \( P < 0.001 \)). The non-response patients were also less likely to be regularly physically active (Table 1).

About two-thirds of the non-response patients (68.5%) had deficient 25(OH)D
concentrations (< 20 ng/ml), which was significantly higher than the percentage of vitamin D deficiency in response patients (Table 2). In the binary logistic regression analysis, vitamin D deficiency was independently associated with higher probability of treatment non-response (OR 11.636, 95% CI 3.966-34.142, P < 0.001). Moreover, a duration of insomnia ≥5 years was significantly associated with a greater probability of treatment non-response (OR 3.625, 95% CI 1.344 – 9.775, P = 0.011, respectively). In addition, higher PSQI and GAD-7 scores at baseline and regular physical activity were associated with a lower probability of treatment non-response (OR 0.784, 95% CI 0.650 - 0.945, P = 0.011; OR 0.792, 95% CI 0.659 - 0.951, P = 0.012; OR 0.260, 95% CI 0.098 - 0.686, P = 0.007, respectively) (Table 3).

4. Discussion

We explored, for the first time, the relationship between serum concentrations of 25(OH)D and chronic insomnia. We found that chronic insomnia patients had lower serum concentrations of 25(OH)D when compared with healthy controls. Moreover, our results indicated that serum 25(OH)D concentrations could possibly emerge be a biological marker of risk for poor treatment outcomes in chronic insomnia patients.

Recently, a growing body of studies has shown that low serum 25(OH)D concentrations is associated with depressive disorder[21], dementia and poor cognitive function[11]. These studies have suggested a possible role of vitamin D in regulating brain function. However, the exact role of vitamin D in the pathophysiology of insomnia remains unclear. Previous animal experiments have reported that nuclear receptors of vitamin D hormone are broadly present in many brain areas, including the hypothalamus, raphe nuclei and substantia nigra, all of which
are thought to play a key role in sleep regulation [22-24]. Vitamin D receptors have also been found in these same brain regions through immunohistochemistry [25]. As mentioned previously, human studies have reported the relationship between low serum 25(OH)D concentrations and sleep disorders. One study showed that vitamin D deficiency is associated with insufficient sleep duration and low sleep efficiency (ratio of total sleep time/nocturnal time spent lying in bed ×100%). Similarly, a negative correlation between 25(OH)D concentrations and the PSQI subscale (sleep duration) score has also been found in premenopausal and postmenopausal women [26]. These studies have provided strong support for the ideal that low serum 25(OH)D concentrations may be involved in the pathophysiology of insomnia.

In our study, the positive association between vitamin D deficiency and treatment non-response at 2 months was found after adjusting for other confounding factors. Insomnia patients with vitamin D deficiency had excessive daytime sleepiness and engaged in less outside activity [27]. This lifestyle may be related to poor sleep hygiene practices (e.g., spending more time in bed to get rest, more daytime napping). According to the two-process model [28], increased time in bed for insomnia patients was associated with more consecutive poor sleep nights due to insufficient sleep drive [29]. Additionally, severe hypovitaminosis D was associated with chronic musculoskeletal pain and physical discomfort, which may exacerbate the poor-quality sleep of insomnia patients [30]. Thus, chronic insomnia patients with vitamin D deficiency may benefit less from the pharmacotherapies for insomnia.

We found that higher PSQI and anxiety scores at baseline were associated with lower probabilities of treatment non-response, which are concordant with previous studies [20,31].
This finding may be due to patients with higher baseline scores being associated with greater opportunity for improvement and greater motivation to overcome insomnia. Our results showed that longer insomnia duration (≥ 5 years) was a risk factor for meeting the non-response criteria. This result is in accordance with an earlier study [32]. It is possible that patients with longer insomnia duration tend to have prior pharmacotherapy experience and benefit less from additional drug therapy. We also demonstrated that regular physical activity was associated with a lower probability of treatment non-response. Several lines of evidence have indicated that long-term moderate or vigorous aerobic exercise is effective at improving sleep quality in chronic insomnia patients [33,34]. However, the intensity of “regular physical activity” in our study may not meet the criterion of “moderate or vigorous aerobic exercise”. Our results also suggest that regular physical activity could be a practical guide for treating chronic insomnia.

Several limitations in this study should be noted. First, we lack polysomnography to provide objective information. However, while polysomnography is not a suggested method for diagnosing insomnia in clinical practice. Second, information about daily sun exposure and dietary intake were not recorded, which may affect serum 25(OH)D concentrations. Third, serum 25(OH)D concentrations were only measured once (at baseline), further researches are required to evaluate how 25(OH)D concentrations change with time after treatment. Fourth, our study solicited chronic insomnia patients from a hospital-based outpatient neurology clinic and they were treated by a single neurologist. Therefore, our findings may not generalize to other chronic insomniacs in the broader community. Finally, the patients in this study did not all receive the same drug treatment. Further prospective
research and randomized controlled trials are required to fully assess whether 25(OH)D concentrations influence the prognosis of chronic insomnia.

Overall, we found that patients with chronic insomnia had lower serum 25(OH)D concentrations when compared with healthy controls. Our study also demonstrates a strong association between serum 25(OH)D concentrations at baseline and the treatment outcome of chronic insomnia at 2 months. In clinical practice, chronic insomnia patients with vitamin D deficiency may be a specific subgroup of the insomniac population that needs additional treatment options, including vitamin D supplement, aerobic exercise training or other non-pharmacological therapy.

Acknowledgment

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Sleep Medicine 12 (2011) 1018.
Table 1 Baseline characteristics of response, non-response and healthy controls groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-Response (N=54)</th>
<th>Response (N=127)</th>
<th>Healthy control (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/40</td>
<td>38/89</td>
<td>32/68</td>
</tr>
<tr>
<td>Age (y), mean ± SD</td>
<td>42.66 ± 10.75</td>
<td>43.37 ± 10.79</td>
<td>44.31 ± 10.33</td>
</tr>
<tr>
<td>BMI (kg/m^2), mean ± SD</td>
<td>21.98 ± 3.84</td>
<td>21.85 ± 3.28</td>
<td>22.10 ± 2.14</td>
</tr>
<tr>
<td>Education (y), median (IQR)</td>
<td>8 (7-13)</td>
<td>8 (6-12)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married (%)</td>
<td>51 (94.4%)</td>
<td>114 (89.8%)</td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of insomnia ≥ 5 years (%)</td>
<td>27 (50.0%)</td>
<td>54 (42.5%)</td>
<td></td>
</tr>
<tr>
<td>Family history of insomnia (%)</td>
<td>16 (29.6%)</td>
<td>34 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>PSQI score at baseline, mean ± SD</td>
<td>14.07 ± 2.53</td>
<td>15.55 ± 2.62</td>
<td></td>
</tr>
<tr>
<td>GAD-7 score at baseline, mean ± SD</td>
<td>7.02 ± 3.70</td>
<td>9.10 ± 4.31</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 score at baseline, mean ± SD</td>
<td>8.87 ± 4.76</td>
<td>10.76 ± 5.01</td>
<td></td>
</tr>
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</table>
Lifestyle and habits

<table>
<thead>
<tr>
<th></th>
<th>Responder (%)</th>
<th>Non-Responder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drinking (%)</td>
<td>4 (7.4%)</td>
<td>17 (13.4%)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>1 (1.9%)</td>
<td>12 (9.4%)</td>
</tr>
<tr>
<td>Regular physical activity (%)</td>
<td>15 (27.8%)</td>
<td>66 (52.0%)</td>
</tr>
</tbody>
</table>

Laboratory variables

| 25(OH)D (ng/ml), mean ± SD | 19.63 ± 7.17a | 24.44 ± 9.58d | 27.17 ± 6.41 |

IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index; GAD-7, Anxiety Disorder Scale-7; PHQ-9, Patient Health Questionnaire-9; 25(OH)D: 25-hydroxyvitamin D

\textsuperscript{a} P < 0.001 compared with Responder; \textsuperscript{b} P < 0.05 compared with Responder;

\textsuperscript{c} P < 0.001 compared with normal controls; \textsuperscript{d} P < 0.05 compared with normal controls.
Table 2 The percentage of vitamin D deficiency in response and non-response patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-Responder (N=54)</th>
<th>Responder (N=127)</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Deficiency (%)</td>
<td>37 (68.5%)</td>
<td>43 (33.9%)</td>
<td>18.46</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-Deficiency (%)</td>
<td>17 (31.5%)</td>
<td>84 (66.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Binary logistic regression model of the clinical determinants of Non-response

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>11.636 (3.966-34.142)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GAD-7 score at baseline</td>
<td>0.792 (0.659 - 0.951)</td>
<td>0.012</td>
</tr>
<tr>
<td>PHQ-9 score at baseline</td>
<td>0.784 (0.650 - 0.945)</td>
<td>0.011</td>
</tr>
<tr>
<td>PSQI score at baseline</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>0.260 (0.098 - 0.686)</td>
<td>0.007</td>
</tr>
<tr>
<td>Duration of insomnia ≥ 5 years</td>
<td>3.625 (1.344 – 9.775)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

GAD-7, Anxiety Disorder Scale-7; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index;
Highlights
• Serum 25(OH)D concentrations in chronic insomnia patients were significantly lower than those of healthy control subjects.
• Non-response patients had significantly lower 25(OH)D concentrations than response patients and the healthy controls. Response patients also had lower 25(OH)D concentrations compared with healthy controls.
• Vitamin D deficiency (< 20 ng/mL) was independently associated with higher probability of treatment non-response at 2 months
• Measurement of serum 25(OH)D concentrations are probably useful for judging treatment outcomes of pharmacotherapy in chronic insomnia patients.