Vitamin D and Schizophrenia: Association, Therapeutic Potential and Mechanisms

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ABSTRACT

Schizophrenia is a severe mental disorder that affects approximately 1% of the U.S population and it is characterized by a wide range of symptoms including hallucination, delusion, and lack of pleasure. It is believed both genetic and environmental influences contribute to schizophrenia onset. Among environmental influences, vitamin D has been extensively studied as a risk factor for schizophrenia. Both developmental and adult vitamin D deficiencies have been demonstrated to be associated with schizophrenia. Developmental vitamin D supplementation during an early year of life could dramatically reduce the rate of schizophrenia development. In addition, adult vitamin D supplementation in schizophrenia patients was shown to decrease the disease’s severity. In this article, we review recent advances in the connection, therapeutic potential, and pathogenetic mechanism of vitamin D in schizophrenia. (Int J Biomed Sci 2022; 18 (4): 66-73)

Keywords: schizophrenia; vitamin D; vitamin D supplementation; 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D3

INTRODUCTION

Schizophrenia is a severe chronic mental disorder that affects approximately 1% of the U.S. population and 24 million people worldwide (1, 2). Schizophrenia has a wide range of symptoms which can be categorized into positive symptoms (the presence of symptoms), negative symptoms (a loss of normal mental activity), and cognitive symptoms (cognitive dysfunctions). The major positive symptoms of schizophrenia include hallucination, delusion, movement disorder, and thought disorder. The negative symptoms refer to affective flattening (reduced or absent expression of effect), social withdrawal, and lack of pleasure and follow-through; while examples of cognitive symptoms consist of cognitive dysfunctions such as loss of short-term and long-term memory (1, 3, 4). The prevalence of schizophrenia appears to be higher among men than in women, and the onset age of the disease also generally occurs earlier for men (around 18-25 years old) compared to women (around 25-35 years old) (5). Schizophrenia is associated with significant morbidity and premature mortality with a typical 20-year shorter life expectancy than the general population (6). Despite over a century of research, the etiology of schizophrenia remains elusive. It is believed that
both genetic susceptibility and environmental influences contribute to schizophrenia onset. Studies have shown that the risk of both dizygotic twins having schizophrenia is 12% to 14%, while monozygotic twins face a higher risk of 48% (7). If both parents have schizophrenia, the possibility of having a kid with schizophrenia would be 48% (7). Environmental factors also play important roles in causing schizophrenia, including childhood trauma (e.g., physical or sexual abuse), culture stress (e.g., migration to new locations), and living environment (8, 9).

Vitamin D is an important nutrient in the body for bone metabolism, calcium homeostasis, and cardiovascular health (10, 11). Vitamin D3, the active form of vitamin D, is synthesized in the skin from 7-dehydrocholesterol in response to UVB light. Subsequently, vitamin D3 is converted to 25-hydroxyvitamin D [25(OH)D] by 25-hydroxylase in the liver. Finally, 25-(OH)D is subjected to further catalysis to make 1,25-dihydroxyvitamin D3 (calcitriol, (1,25(OH)2 D3)) in the kidney (Figure 1) (12). Recent studies have shown that vitamin D deficiency is associated with cognitive dysfunction, a key element of schizophrenia (13–15), and the administration of vitamin D supplements alleviate schizophrenia symptoms (16). In this review article, we provide a concise review of the association, therapeutic potential, and molecular mechanisms of vitamin D with schizophrenia.

ASSOCIATION OF VITAMIN D LEVELS WITH SCHIZOPHRENIA

Developmental vitamin D deficiency and schizophrenia

The hypothesis that low maternal vitamin D levels may lead to an increased risk of schizophrenia can be dated back two decades ago (17, 18). Many studies have reported the epidemiology of schizophrenia and its variations based on environmental factors such as seasonality of births, birthplace, and migration patterns. For instance, Mortensen et al analyzed the birthplace and birth season among 2669 cases of schizophrenia in Danish people born between 1935 and 1978. They found that the risk of schizophrenia was associated with the degree of urbanization of the birthplace (the highest risk of schizophrenia for births in capital cities vs. the lowest for births in rural areas) and the birth seasons (the highest risk rate of schizophrenia for births in February and March vs. the lowest risk rate for births in August and September) (19). Similar observations have been reported in many other studies, supporting the hypothesis that reduced sunlight exposure due to birthplace and birth season leads to vitamin D deficiency and subsequent risk of developing schizophrenia (20, 21). As the hypothesis was formed, more systematic experimental and analytical studies were conducted to examine the link between vitamin D deficiency and the risk of schizophrenia. McGrath et al first studied vitamin D levels in the neonatal blood spots stored at the Danish Biobank Register since 1981 with 424 individuals diagnosed with schizophrenia and 424 controls with matched sex and dates of birth. They found that both low and high concentrations of neonatal vitamin D are associated with increased risks of schizophrenia (22). In a pilot study of maternal vitamin D correlation with the risk of schizophrenia development, McGrath and colleagues measured 25(OH)D concentrations in the sera taken during the third trimester in the United States of America, the 25(OH)D level comparison was made between mothers of individuals with schizophrenia (n=26) and mothers of unaffected controls (n=51) (23). The study result indicated that though maternal vitamin D does not operate as a continuous graded risk factor for schizophrenia, low levels of maternal vitamin D in the black subgroup may be associated with an increased risk of schizophrenia (23). Recently, Eyles et al performed a larger case-control study of 1301 schizophrenia cases and 1301 controls with matched sex and ages. Their result demonstrated that only those in the lowest quintile (<20.4 nmol/L) of maternal vitamin D had a significantly increased risk of schizophrenia (incidence rate ratio IRR = 1.44, 95%CI: 1.12–1.85) compared to the reference quintile (Table 1) (24).
Adult vitamin D deficiency and schizophrenia

Other than studies of the relationship between developmental vitamin D deficiency and schizophrenia, multiple reports have studied adult vitamin D deficiency in patients with schizophrenia as well. Itzhaky and colleagues recruited 50 patients with schizophrenia and 50 healthy control subjects. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia was used to assess schizophrenia on the day when the blood samples were drawn to measure serum concentrations of 25(OH)D by LIAISON 25-OH vitamin D (DiaSorin) immunoassay (25). Lower serum vitamin D concentrations were detected among patients with schizophrenia (15.0 ± 7.3 ng/ml) compared to healthy controls (20.2 ± 7.8 ng/ml, P<0.05) although no correlation between disease activity measured by the PANSS score and vitamin D levels was observed (25). In another study, Bulut et al studied the serum 25(OH)D levels in 80 patients diagnosed with schizophrenia and 74 age- and sex-matched healthy controls (26). They measured schizophrenia symptom severity by using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). Statistically significant differences were found between the vitamin D levels and the total SANS, affective flattening, SAPS, bizarre behavior, and positive formal thought disorder scores of schizophrenia patients (p=0.019, p=0.004, p=0.015, p=0.009, and p=0.019, respectively) (26). There are negative correlations between 25(OH)D levels and SANS total points (r=-0.232, p=0.038), 25(OH)D levels and attention points (r=-0.227, p=0.044) and 25(OH)D levels and positive formal thoughts (r=-0.257, p=0.021). Their result supports the relationship between lower levels of vitamin D and the occurrence of positive and negative symptoms, along with increased severity of symptoms at lower levels of vitamin D (26).

VITAMIN D TREATMENT FOR SCHIZOPHRENIA

While studies have demonstrated the potential connection of vitamin D deficiency with schizophrenia, some researchers have focused on determining the effects of vitamin D supplementation on preventing schizophrenia, as well as the possible potency of vitamin D in reducing the prevalence of schizophrenia and its symptoms (Table 2). For instance, among the 9,114 subjects drawn from the Northern Finland 1966 Birth Cohort, McGrath et al collected data about the frequency and dose of vitamin D supplementation during the first year of life and the occurrence of schizophrenia by the age of 31 years old (27). They reported that men who took vitamin D supplements in their early years—more precisely, within the first year of life—have a considerably lower risk of developing schizophrenia. Compared to individuals who received less than 2000 IU of vitamin D per day, the risk of schizophrenia was reduced by 77% in males who received at least 2000

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<tr>
<td>McGrath et al (19)</td>
<td>848</td>
<td>A total of 424 individuals with schizophrenia and 424 controls matched for sex and date of birth.</td>
<td>Denmark</td>
<td>Both low and high concentrations of neonatal vitamin D are associated with increased risk of schizophrenia</td>
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<td>McGrath et al (23)</td>
<td>77</td>
<td>Mothers of individuals who have schizophrenia and non-affected controls</td>
<td>United States</td>
<td>Low levels of maternal vitamin D are associated with an increased risk of schizophrenia</td>
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<td>Eyles et al (24)</td>
<td>2602</td>
<td>Those born in Denmark between 1981–2000 who received a diagnosis of schizophrenia. Controls were individually matched on sex and date of birth. They were alive and free of schizophrenia at the time of onset of the matched cases.</td>
<td>Denmark</td>
<td>Only those in the lowest quantile of vitamin D had a significantly increased risk of schizophrenia</td>
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<td>D. Itzhaky et al (25)</td>
<td>133</td>
<td>50 patients with schizophrenia, 33 patients with major depression, and 50 controls with no major psychopathology.</td>
<td>Israel</td>
<td>Serum vitamin D levels were lower in patients with schizophrenia as compared to patients with depression and to healthy controls.</td>
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IU/day. However, no significant associations between either the frequency or dose of vitamin D supplements and schizophrenia were found in females for unknown reasons (27). As Finland lies between 60° and 70° North latitudes, the ultraviolet radiation from October to March would be insufficient to produce vitamin D from actinic sources, resulting in a high prevalence of hypovitaminosis D, which is thought to be linked with the winter-spring excess of schizophrenia births (28, 29). Interestingly, the winter-spring excess of schizophrenia births in Finland has declined significantly since the 1950s, which coincides with a public health campaign to use high-dose vitamin D supplements during the first year of life in the 1960s(30). Those results suggest that vitamin D supplementation during the early years of life could reduce the incidence rate of schizophrenia development (27-30).

Subsequently, more studies have demonstrated that vitamin D supplementation to schizophrenia patients could reduce schizophrenia severity and activities. For instance, Neriman et al conducted a study with 40 schizophrenia patients whose serum 25(OH)D reached optimal levels (>30 ng/mL) after oral administration of vitamin D in Turkey (31). In brief, 50,000 IU oral vitamin D was given once a week for eight weeks to the patients whose vitamin D levels were <20 ng/mL (vitamin D deficiency), and 1500 IU oral vitamin D was given daily to the patients whose vitamin D level was between 20 and 29.99 ng/mL (vitamin D insufficiency) (31). Patients whose serum vitamin D level could not reach >30 ng/mL were given additional doses until the optimal level was reached. In this study, the severity of their schizophrenia symptoms (positive, negative, and cognitive) was measured using SANS, SAPS, and WCST (Wisconsin Card Sorting Test) respectively. They observed that the SANS and SAPS scores after the vitamin D supplementation were both significantly lower than those prior to the vitamin D supplementation. Furthermore, the total attention score also improved significantly after the vitamin D supplementation (31). All the results

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<tr>
<td>McGrath J et al (27)</td>
<td>9,114</td>
<td>Schizophrenia occurrence by age of 31 years old</td>
<td>Northern Finland</td>
<td>In males, the use of least 2000 IU of vitamin D reduced the risk of schizophrenia.</td>
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<td>Neriman et al (31)</td>
<td>40 (34 males and 6 females)</td>
<td>Schizophrenia patients visiting the Community Counseling Service at Trabzon Kanuni Training and Research Hospital</td>
<td>Turkey</td>
<td>Schizophrenia scores and total attention scores after the vitamin D supplementation were lower than they were prior to the vitamin D supplementation.</td>
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<td>Ghaderi et al (32)</td>
<td>60</td>
<td>Chronic schizophrenia patients</td>
<td>Iran</td>
<td>Probiotics and vitamin D for 12 weeks had beneficial effects on the general and total PANSS score and metabolic profiles in chronic schizophrenia.</td>
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<td>Fond et al (33)</td>
<td>140</td>
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<td>Sheikhmoonesi et al (34)</td>
<td>80</td>
<td>Patients with chronic stable schizophrenia with residual symptoms and Vitamin D deficiency</td>
<td>Iran</td>
<td>No relationship was found between serum vitamin D level changes and the improvement of negative and positive symptoms in schizophrenic patients.</td>
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<td>Krivoy et al (35)</td>
<td>47</td>
<td>Schizophrenia patients who had been maintained on clozapine treatment for at least 18 weeks and had low levels of vitamin D (&lt; 75 nmol/l) and total PANSS scores &gt; 70</td>
<td>Israel</td>
<td>Vitamin D supplementation was associated with a trend toward improved cognition but did not affect psychosis, mood, or metabolic status.</td>
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in this study have shown that vitamin D supplementation can alleviate the positive, negative, and cognitive symptoms of schizophrenia (31). Similarly, in a randomized controlled trial, 60 individuals with chronic schizophrenia were randomly assigned to receive either a placebo (n=30) or 50,000 IU of vitamin D3 every two weeks along with 8×10^9 CFU of probiotics every day (n=30) for 12 weeks (32). The co-supplementation of vitamin D and probiotics employed in this study was proven to greatly improve both the general and total PANSS scores (-7.4 ± 8.7 vs. -1.9 ± 7.5), suggesting that vitamin D supplementation can improve schizophrenia conditions (32).

In addition, vitamin D3 supplementation is linked with reduced depressive symptoms in schizophrenia. In a study with 140 schizophrenia patients between 2015 and 2017 in the national FondaMental Expert Center in France, hypovitaminosis D (serum 25(OH)D level < 25 nM) was identified in 21.4% of the schizophrenia patients who had not received any vitamin D supplementation in the past 12 months (33). With a multivariate analysis, researchers found that hypovitaminosis D is significantly associated with higher depressive symptoms and current anxiety disorder respectively, independently of age and gender. On the other hand, schizophrenia patients who received vitamin D supplementation in the prior 12 months showed a great reduction in depressive symptoms and current anxiety disorder (33). In another study, Sheikhoonesi et al. injected vitamin D3 (300,000 IU/mL in sesame oil) intra-muscularly twice for 3 months into male Iranian schizophrenia patients, PANSS was then assessed in the fourth month. They found that vitamin D3 injection did not significantly improve the PANSS score (34). However, it is worth noting that vitamin D3 was injected only twice in 3 months, which may be insufficient to result in measurable improvements in schizophrenia conditions (34) the aim was to determine whether adding vitamin D to the standard therapeutic regimen of schizophrenic male patients with inadequate vitamin D status could improve some aspects of the symptom burden or not. This study was an open parallel label randomized clinical trial. Eighty patients with chronic stable schizophrenia with residual symptoms and Vitamin D deficiency were recruited randomly and then received either 60,000 IU Vitamin D injection once along with their antipsychotic regimen or with their antipsychotic regimen only. Serum vitamin D was measured twice: first at the baseline and again on the fourth month. Positive and Negative Syndrome Scale (PANSS). Likewise, Krivoy conducted a small size clinical trial to evaluate the effect of vitamin-D supplementation on schizophrenia patients who received clozapine drug treatment in Israel (35). They recruited 47 clozapine-treated chronic schizophrenia patients with low serum vitamin-D levels. 24 patients were randomly assigned to receive weekly oral drops of vitamin D (14,000 IU) whereas 23 patients received weekly oral drops of placebo for 8 weeks. Patients’ mental statuses were assessed every two weeks with PANSS, Calgary Depression Scale, and Montreal Cognitive Assessment (35). The researchers found a trend toward improved cognition in schizophrenia patients following vitamin D supplementation, although it was not statistically significant in comparison to the placebo-treated group, which may be attributed to the small sample size in this study (35).

**POTENTIAL MECHANISMS OF VITAMIN D IN SCHIZOPHRENIA**

**Developmental vitamin D deficiency leads to abnormal brain structure and impairs early brain function**

Animal studies have shown that vitamin D deficiency during gestation alters normal brain development, which may impair early brain function. Ko et al. examined the role of vitamin D in influencing apoptosis and cell proliferation in the developing rat brain (36). 6 weeks before mating and throughout pregnancy, Sprague-Dawley female and male rats used for breeding were maintained on a vitamin D-depleted diet with an incandescent light source that filters UVB rays (280–232 nm) to prevent vitamin D production. In comparison, control rats were given conventional rat food under normal lighting conditions. The study’s findings revealed that in comparison to the control animals, rat embryos and pups with maternal vitamin D deficiency had a considerably lower number of apoptotic cells and more mitotic cells in their brains (36). In consistency, Eyles et al. further confirmed that a lack of vitamin D during pregnancy increased cell proliferation in the dentate, hypothalamus, and basal ganglia/amygdala in neonatal rats, resulting in abnormal brain structure with larger lateral ventricles and altered brain shape (37). More specifically, vitamin D-depleted pups had heavier brains, larger, longer brain cortices and lateral ventricles. Furthermore, in all four of the examined brain areas, vitamin D deficiency also appeared to diminish expressions of glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and the nonselective neurotrophic receptor (p75NTR) in neonatal rat brains. The results suggest a correlation between developmental vitamin D deficiency and abnormality in the brain (37).
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Developmental vitamin D deficiency alters dopaminergic neuron development

Additionally, vitamin D deficiency can alter the development of dopaminergic neurons and neurotransmitter expression (38). Cui et al. studied Nurr1 and p57Kip2, two genes essential for DA cell differentiation and maturation in groups of female Sprague-Dawley rats who received either a diet rich (1000 IU/kg) or deficient (0 IU/kg) in vitamin D (39). Their study showed that Nurr1 and p57Kip2 expression levels in the mesencephalon (midbrain) were significantly reduced in the developmental vitamin D-deficient embryos, supporting that prenatal vitamin D insufficiency alters the proper dopaminergic development (39). Moreover, developmental vitamin D deprivation impacts neonatal rat brain neurotransmitter systems. For example, rats with DVD deficiency have consistently been shown to have altered dopamine signaling and serotonin turnover (40, 41). Kesby et al. assessed regionally specific effects of vitamin D deficiency on neurotransmitters in an experiment with Sprague-Dawley rats (42). The result showed that developmental vitamin D deficiency leads to regional abnormalities and induces disruptions to several developmental neurotransmitter systems in neonates relevant to schizophrenia in the developing rat brain (42). There were also significant surges in the levels of dopamine and noradrenaline in the hippocampus, thalamus, and midbrain in developmental vitamin D-deficient rats compared with control neonates. However, compared to control neonates, developmental vitamin D-deficient neonates displayed considerably lower levels of serotonin in the caudate putamen and basal ganglia as well as a significant drop in baseline glutamine content in all regions except the midbrain (42).

Developmental vitamin D deficiency leads to placental complications

Lately, new studies indicated that vitamin D deficiency is associated with placenta-mediated complications (PMC), and placenta health could influence the expression of the genetic risk for schizophrenia. For instance, after studying 182 patients with a high risk of developing or recurring PMC (e.g., obesity, maternal age younger than 18 years or older than 38 years old, chronic kidney disease and hypertension) who received five blood tests, Raia-Barjat et al. found that vitamin D-deficient patients had a five-times greater risk of developing PMCs at 32 weeks of pregnancy compared to patients with normal vitamin D levels. It is concluded that vitamin D plays a crucial role in placental performance, and vitamin D deficiency leads to higher risks of PMCs (43). Maternal vitamin D insufficiency could increase the risk of preeclampsia. Aim of the study was to evaluate the relationship between vitamin D status and the occurrence of placenta-mediated complications (PMCs). Chen et al. conducted a study with mice to further inspect the effects of gestational vitamin D deficiency on fetal intrauterine growth restriction (IUGR), in which the fetuses do not perform their genetic growth potential (44). They found that placental proliferation was inhibited, and placental weight was decreased in vitamin D-deficient diet-fed mice likely through inducing placental inflammation. Additionally, gestational vitamin D deficiency was shown to hinder placenta development and function as protein levels of placental Glut1 and Snat2 mRNAs were reduced in the vitamin D deficiency group (44). Furthermore, an epidemiological study conducted by Ursini et al. explored the influence of the placenta on the risk of schizophrenia (45). After analysis of independent samples from the U.S., Italy, Germany, and Japan, they found that the expression of genetic risk for schizophrenia was significantly high in the placenta from complicated pregnancies in comparison with normal pregnancies. Expression of genetic risk for schizophrenia was also differentially upregulated in placentae from male compared with female offspring during complicated pregnancies and under duress (45). In conclusion, vitamin D deficiency may be indirectly associated with schizophrenia through placenta complications (43-45).

Adult vitamin D in schizophrenia

In contrast to extensive biological studies of developmental vitamin D with schizophrenia, the mechanism of adult vitamin D deficiency for schizophrenia has not been well studied. Groves et al. first examined the effect of adult vitamin D deficiency on behavior and brain function in mice (41). C57BL/6J and BALB/c mice were fed either a normal diet or a vitamin D deficient diet for 10 weeks before and during behavioral testing. The result showed that in general, adult vitamin D deficiency led to lower expression levels of the 65 and 67 kDa isoforms of glutamic acid decarboxylase (GAD65/67), in brain tissue, which are relevant to several neuropsychiatric conditions including schizophrenia (46).

A similar study was conducted by Al-Amin and colleagues in BALB/c mice, and the result demonstrated that adult vitamin D deficiency led to altered hippocampal-dependent spatial learning as well as a disrupted network centered on the right hippocampus with connection deficits (47). Although this study did not establish a direct relationship between adult vitamin D deficiency and schizophrenia,
phrenia, overall, results from this study suggested that adult vitamin D deficiency serves as an important factor in hippocampal-dependent learning and memory formation (47). Moreover, a study conducted by Taghizadeh et al on the spatial performance of adult rats exemplified a similar outcome (48). Adult vitamin D-deficient rats performed the worst in the behavioral test, indicating that adult vitamin D deficiency was detrimental to spatial task learning (48).

CONCLUSION

Preceding studies regarding birthplaces and birth seasons have sparked the hypothesis regarding the association between neonatal vitamin D deficiency and schizophrenia development. Additional experimental and analytical studies have identified that developmental vitamin D deficiency enhances the signs and risks of schizophrenia. In consistence, vitamin D supplementation in the early years of life dramatically reduces the risk of schizophrenia in adulthood, and Vitamin D treatment has reduced schizophrenia patients’ symptoms and severity. Though the exact pathogenesis by which vitamin D deficiency leads to schizophrenia has not been well understood, recent studies have highlighted that developmental vitamin D deficiency results in abnormal structure, impairments, complications of the brain, as well as abnormal development of dopaminergic neurons. In addition, studies have indicated that developmental vitamin D deficiency may be indirectly associated with schizophrenia through placenta complications. Nevertheless, studies investigating the mechanism of adult vitamin D deficiency with schizophrenia are few, and further investigations into this aspect are needed. Moreover, clinical trials at larger scales to study vitamin D supplementation for schizophrenia prevention and its severity are warranted.

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REFERENCES


16. Eyles DW, Burne THJ, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol. 2013 Jan; 34 (1): 47–64.


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