

Research Paper: High-dose Vitamin D Supplementation and Improvement in Cognitive Abilities, Insomnia, and Daytime Sleepiness in Adolescent Girls



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Citation: Bahrami, A., Rezaeitalab, F., Farahmand, S. K., Mazloum Khorasani, Z., Arabi, S. M., & Bahrami-Taghanaki, H. R., et al. (2020). High-dose Vitamin D Supplementation and Improvement in Cognitive Abilities, Insomnia, and Daytime Sleepiness in Adolescent Girls. *Basic and Clinical Neuroscience*, 12(3), 339-348. <http://dx.doi.org/10.32598/bcn.2021.1910.1>

doi <http://dx.doi.org/10.32598/bcn.2021.1910.1>



Article info:

Received: 27 Jun 2019
First Revision: 10 Jul 2019
Accepted: 02 Sep 2020
Available Online: 01 May 2021

Keywords:

Vitamin D, Cognition, Adolescents, Sleepiness, Insomnia

ABSTRACT

Introduction: Vitamin D may affect the modulation of signaling pathways in the central nervous system. We aimed to evaluate the effect of high-dose vitamin D supplementation on neuropsychological functions in female adolescents.

Methods: We studied the effects of 9 weeks of vitamin D supplementation (50000 IU vitamin D3 [cholecalciferol]/week) on cognitive abilities and sleep disorders in 940 adolescent girls.

Results: Oral vitamin D supplementation improved cognitive abilities, including memory, inhibitory control, selective attention, decision making, planning, sustained attention, and cognitive flexibility in healthy adolescent girls ($P < 0.001$). The prevalence of subjects with insomnia after intervention fell from 15.0% to 11.3%. Similar results were also found for the prevalence of sleepiness (15.6% reduced to 14.7%), or cases with both insomnia and sleepiness (8.0% reduced to 6.1%; $P < 0.05$).

Conclusion: High dose of vitamin D can improve cognitive abilities and alleviate insomnia and daytime sleepiness in adolescent girls. Further investigations are required on different population groups (age and gender) to determine the sustainability of these effects. The value of vitamin D therapy in other neurological disorders would also be of research interest.

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Highlights

- Oral vitamin D supplementation improved cognitive abilities, including memory, inhibitory control, selective attention, decision making, planning, sustained attention, and cognitive flexibility in healthy adolescent girls.
- Vitamin D supplementation improved insomnia in adolescent girls.
- Vitamin D supplementation improved sleepiness in adolescent girls.

Plain Language Summary

The effect of a high dose supplement of the fat soluble vitamin D given for 9 weeks, on sleep quality, and several other psychological parameters, was assessed in 940 adolescent girls from northwestern Iran. Vitamin D supplementation was associated with a significant reduction insomnia and sleepiness in participants at the end of the trial.

1. Introduction

Nuclear steroid hormone Vitamin D (VitD) contributes to various physiological processes in the body. The role of VitD in calcium homeostasis has already known. Also, VitD affects neuronal functioning (Eyles et al., 2009; McCann & Ames, 2008; McGrath, Feron, Eyles & Mackay-Sim, 2001). VitD exhibits neurosteroid properties, essential to protect the Central Nervous System (CNS), and helps in neurotransmission, neuroimmunomodulation, and brain processes (Briones & Darwish, 2012).

Vitamin D Receptors (VDR) are widely distributed in many cell types of the human brain, such as neurons and glial cells. High levels of VDR is found in the cortex and hippocampus (Eyles, Smith, Kinobe, Hewison & McGrath, 2005; Langub, Herman, Maluche & Koszewski, 2001; Prüfer, Veenstra, Jirikowski & Kumar, 1999), which are essential areas for regulation of cognitive functions, such as learning, memory, and behavior (Becker, Eyles, McGrath & Grecksch, 2005). Moreover, enzyme (1- α -hydroxylase) related to the synthesis of the active form of VitD is prevalent in the brain, and its gene expression has been found in neural tissues (Zehnder et al., 2001). VDR also contributes to neuroprotective pathways, decreasing oxidative damages and amyloid- β formation and accumulation (Morley, 2014). Animal studies have shown that VitD is crucial for brain development (Eyles et al., 2009). These studies have reported that VitD may support the structure and integrity of neurons within neurotrophin synthesis and detoxification pathways, which is mandatory for neuronal survival (Kang & Schuman, 2000).

Inadequate VitD levels in prenatal rats dysregulate 36 brain proteins implicated in multiple biological activities, such as oxidative phosphorylation, redox balance, cytoskeleton reservation, post-translational modifications, synaptic plasticity, calcium homeostasis, and neurotransmission in adult (Almeras et al., 2007). Furthermore, evidence shows that VitD deficiency may cause mental disorders such as major and minor depression, schizophrenia, anxiety, and sleep disorders (Garcion, Wion-Barbot, Montero-Menei, Berger & Wion, 2002; Gominak & Stumpf, 2012; Hoogendijk et al., 2008; Jorde, Waterloo, Saleh, Haug & Svartberg, 2006). Risen dietary consumption of VitD has been related to fewer incidences of self-reported psychotic-like events (Hedelin et al., 2010).

Recent studies have suggested a negative association between VitD status and adverse sleep outcomes (Bellia et al., 2013; Khoo et al., 2011). The negative impacts of sleep disorders include sleepiness, neurocognitive deficits, decrease mental performance, daytime fatigue, and altered mood in adolescents. In recent years, sleep disorders have become very common worldwide and contribute to the etiology of heart disease, diabetes, depression, and other complications (Bagai, 2010; Skaer & Sclar, 2010).

The effects of VitD on cognitive function and sleep patterns have been reported in several studies, but the results of these studies are inconsistent (Rossom et al., 2012; Stein, Scherer, Ladd & Harrison, 2011). Epidemiological studies show an association between low concentration of VitD and impairments in cognitive performances such as memory and orientation (Llewellyn, Langa & Lang, 2009; Przybelski & Binkley, 2007; Wilkins, Sheline, Roe, Birge & Morris, 2006), psychomotor speed, and executive function (Buell et al., 2009; Lee et al., 2009), also diagnosis of vascular dementia and

Alzheimer disease (Buell et al., 2010). However, other studies found no relationship between VitD levels and performance on cognitive testing (Slinin et al., 2010), or they showed worse cognitive function by the elderly individuals in the high 25-hydroxy vitamin D [25(OH)D] quintile (McGrath et al., 2007). Also, it has been reported that individuals with sleep disorders have lower serum 25(OH)D levels (McCarty, Reddy, Keigley, Kim & Marino, 2012; Mete et al., 2013).

We have previously shown that VitD supplementation positively affects systemic inflammation, cardio-metabolic profile, and mood or emotional performance in adolescents (Bahrami et al., 2018; Khayyat-zadeh et al., 2018; Tabatabaeizadeh et al., 2017). The present study aimed to further assess supplementation with high dose VitD on cognitive abilities, insomnia, and daytime sleepiness in adolescents.

2. Methods

2.1. Study design

This study was performed in the cities of Mashhad and Sabzevar, Iran, between January and April 2015, as described previously (Khayyat-zadeh et al., 2018; Tabatabaeizadeh et al., 2017). In a large VitD project, 1026 adolescents aged between 12 and 18 years were called. Of whom, 988 met the inclusion criteria. All participants received 9 50000 IU of VitD capsules for 9 weeks (1 per week). Finally, 940 adolescents completed the trial, with a dropout rate of 4.8%. The Ethics Committee approved the study and informed written consent was provided by all participants and their parents (IR.MUMS.FM.REC.1395.12).

2.2. Study instruments

Assessment of cognitive abilities and sleep disorders was performed by standard self-report questionnaires mentioned as follows. An expert assistant aids participants to fulfill all of the questions.

2.3. The Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) questionnaire is a reliable instrument that yields a quantitative index of perceived insomnia severity. The instrument involves 7 items focusing on sleep disorder severity, sleep-related satisfaction, and anxiety related to the sleeping problem. Each item is rated on a 5-point Likert-type scale (0-4) and provides a total score ranging from 0 to 28. Higher scores indicate more severe insomnia. Scores may be categorized as 0-7 (no clinically significant insomnia), 8-14

(sub-threshold insomnia or mild insomnia), 15-21 (moderate insomnia), and 22-28 (severe insomnia). ISI-Persian was previously validated among Iranian subjects and was found to have a high internal consistency (The Cronbach alpha= 0.8 and test-retest reliability = 0.7) (Yazdi, Sadeghniaat-Haghighi, Zohal & Elmizadeh, 2012).

2.4. Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a questionnaire-derived scale of sleepiness that can assess the degree of daytime sleepiness. It is an 8-item questionnaire scored on a 4-point Likert-type scale that measures the habitual likelihood to fall asleep in common situations of daily living. The total score ranges from 0 to 24. Normal is less than 10. Mild to moderate obstructive sleep apnea get a score between 10 and 16. Also, severe obstructive sleep apnea or narcolepsy scores over 16. ESS has been validated and found to have a high internal consistency (the Cronbach alpha= 0.88) and acceptable test-retest reliability ($r=0.81$; 95% confidence interval 0.74-0.86, $P<0.001$) among Iranian population (Sadeghniaat Haghighi et al., 2013).

2.5. Cognitive abilities task

Cognitive performances were evaluated using the Cognitive Abilities Questionnaire (CAQ), which comprises 30 items. Each item is rated on a 5-point scale (1-5) and summed up to provide a total score ranging from 30 to 150. The validity of CAQ with high internal consistency (the Cronbach $\alpha=0.83$) and good test-retest reliability ($r=0.86$) have been established in Iranian population (Nejati, 2013). Higher scores represent better cognition abilities. The CAQ assesses memory, inhibitory control, selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility.

2.6. Depression and aggression

To assess the score of depression, the subjects were asked to complete the Beck depression inventory II (BDI II) questionnaire (Beck, Steer & Brown, 1996). Higher scores represent a high degree of depression. The validity of the BDI Persian version with high internal consistency (the Cronbach $\alpha=0.87$) and good test-retest reliability ($r=0.74$) has been established in Iranian students (Mohammadi, 2007).

2.7. The Buss-Perry Aggression Questionnaire (BPAQ)

The Buss-Perry Aggression Questionnaire (BPAQ) is a 29-item questionnaire, which evaluates four aggression scores of physical aggression, verbal aggression, anger, and hostility. They are scored with a 5-point rating sys-

tem. It was used to determine the aggression level of the subjects (Elliott, Baughan & Sexton, 2007). A high BPAQ score indicates higher aggression. The test-retest reliability and validity of this questionnaire have been verified among the Iranian population (Motevalian, Asadi-Lari, Rahimi & Eftekhar, 2011).

2.8. Vitamin D measurements

Fasting blood samples were collected in the early morning at baseline and post nine weeks' trial, after a 12 hour overnight fasting. Blood samples were centrifuged (Hettich model D-78532) to separate serum. An Electrochemical-Luminescence (ECL; Roche) method was used to measure serum 25(OH)D.

2.9. Assessment of other variables

An expert interviewer collected demographic data, and anthropometric parameters were determined using the standard techniques at baseline and after 9 weeks of intervention. The question related to smoking was, "How many hours are you exposed to cigarettes?" If reported 30 minutes and above, the subject was considered exposed to smoking. Physical activity was measured by a validated questionnaire and represented as Metabolic Equivalents (METs) in hours/day (Delshad et al., 2015).

2.10. Statistical method

The Kolmogorov-Smirnov test was used to determine whether the variables had a normal distribution. Results were expressed as frequency, percentage, and Mean±Standard Deviation. The Chi-square or ANOVA tests and post hoc Turkey's test were applied to compare quantitative variables in different subject groups (insomnia, sleepiness, both insomnia, and sleepiness, as well as normal), followed by Tukey HSD. Cochran's Q tests or paired-sample t-test was used to compare variables at baseline and after the intervention. $P < 0.05$ was set at statistical significance in all tests. SPSS for Windows (v. 16, SPSS Inc., Chicago, IL) was used for statistical analysis.

3. Results

A total of 940 subjects were entered the study. At baseline, 222 participants presented some degree of sleepiness (ESS score ≥ 10), and 216 subjects presented some degree of insomnia (ISI score ≥ 8). Altogether, 15.0%, 15.6%, and 8.0% of subjects had some degree of insomnia, sleepiness, both insomnia, and sleepiness, respectively. In contrast, 61.4% had no insomnia and or

sleepiness. Baseline characteristics of responders who completed the intervention are presented in Table 1.

Analysis of Variance (ANOVA) test results showed the four groups of participants (insomnia, sleepiness, both insomnia, and sleepiness, or control) were well-matched regarding age, body mass index, and physical activity. The subjects with some degree of insomnia and daytime sleepiness are more exposed to smoke than normal subjects ($P=0.005$). Furthermore, the subjects with both insomnia and sleepiness have higher depression and aggression scores than the normal population ($P < 0.05$; Table 1).

During and after the supplementation period, no subject reported any significant adverse effects. The Mean±SD serum 25(OH)D level exhibited a significant increase from 9.46 ± 8.83 ng/mL at baseline to 35.91 ± 15.56 ng/mL after supplementation.

After VitD supplementation, significant improvements were seen in most cognitive abilities, including scores at the memory, inhibitory control and selective attention, decision making, planning, sustained attention, and cognitive flexibility after supplementation ($P < 0.001$). But the positive effect on social cognition was not significant (Table 2).

VitD supplementation caused to significant reduction in total score of insomnia in cases with insomnia (9.2 ± 5.1 to 5.7 ± 6.3 ; $P < 0.001$). Day time sleepiness score was also decreased after supplementation in adolescents with some degree of sleepiness (7.5 ± 3.6 to 6.6 ± 4.4 ; $P < 0.001$).

At baseline, the prevalence of subjects with insomnia alone was 15.0%, while this value after supplementation was decreased to 11.3%. Similar results were also found for the prevalence of subjects with only sleepiness (15.6% reduced to 14.7%), and the cases with both insomnia and sleepiness (8.0% reduced to 6.1%), while in normal cases, the sleep disorders increased from 61.4% to 67.9% after supplementation ($P=0.003$; Table 3).

4. Discussion

This interventional study is the first to investigate the effects of high-dose VitD supplementation on cognitive abilities and sleep disorders. The results showed that VitD supplementation significantly improved subjective measures of insomnia, daytime sleepiness, and cognitive abilities such as memory, inhibitory control, and selective attention, decision making, planning, sustained attention, and cognitive flexibility in adolescent girls.

Table 1. Demographic, clinical, and psychological characteristics of study participants at baseline

Variables	Mean±SD				p*
	Normal 577(61.4)	Insomnia 141(15.0)	Sleepiness 147(15.6)	Insomnia + Sleepiness 75(8.0)	
Age (y)	14.4±1.5	14.7±1.6	14.8±1.5	14.6±1.5	0.07
BMI (kg/m ²)	21.1±4.3	21.5±4.9	21.5±3.9	20.6±3.9	0.385
Smoking exposure No. (%)	264 (28.1)	389 (41.4)	336 (35.7)	368 (39.2)	0.005
Physical activity (MET-h/week)	45.2±3.4	45.2±3.1	45.5±2.6	46.0±4.6	0.45
Depression (score)	8.7±8.0	14.8±10.9	11.6±8.8	16.9±9.0	<0.001 ^{α,β,γ,λ,μ}
Aggression (score)	75.7±20.8	81.4±18.6	83.5±19.6	85.3±18.5	<0.001 ^{α,β,γ}

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* Using the Chi-square test (for categorical variable) and ANOVA test and Post hoc Turkey's test (for normally distributed variable);

α: Significant between the normal group and insomnia group;

β: Significant between the normal group and sleepiness group;

γ: Significant between the normal group and insomnia+ sleepiness group;

λ: Significant between the insomnia group and sleepiness group;

μ: Significant between the sleepiness group and insomnia + sleepiness group.

The present study was conducted to validate or refute the effects of VitD supplementation on the cognitive function observed in previous studies (van der Schaft et al., 2013). This study used a large sample size with a rigorous method to assess cognitive abilities. The results are consistent with the amount of data indicating that low VitD status is associated with impairments in cognitive function (Lanham-New et al., 2011; Vieth et al., 2007). The neurocognitive effect of VitD is well-supported. The VDR and catalytic enzymes are present in the brain areas involved in forming new memories, processing, and complex planning (Buell & Dawson-Hughes, 2008). VitD is neuroprotective because it modulates the expression of enzymes (tyrosine hydroxylase) related to dopamine's synthesis and norepinephrine/epinephrine. Also, it enhances neuron survival through the prevention of oxidative pathways responsible for free radical production in the brain via the elevation of antioxidant (γ-glutamyl transpeptidase) generation and the suppression of the synthesis of inducible Nitric Oxide Synthase (iNOS), a toxic enzyme for the brain (Vaidya & Williams, 2012). The Institute of Medicine (2011) claimed a biologically confirmed association between VitD level and brain-related outcomes.

A wealth of evidence supports that low vitamin D may be associated with greater odds of cognitive impairment and reduced cognitive functioning in older adults (Breitling et al., 2012; Llewellyn, Lang, Langa & Melzer, 2011; Przybelski & Binkley, 2007). In HIV-

positive patients, severe VitD deficiency was reported to be independently related with a higher odds of neurocognitive decline (OR=2.1; 95% CI:1.04–4.05) (Vergori et al., 2019). Low serum 25(OH)D concentration may independently predict worsening cognitive functions in diabetic patients (Rui-hua, Yong-de, Xiao-zhen, Chen & Bin, 2019). However, there are some discrepancies in the study results. Some studies have examined the association between VitD status and cognitive functions in young adults with different results (Hansen, Bakke, Dahl & Thayer, 2011; Lašaitė, Gailyte, Puzinas, Preikša & Kazanavičius, 2011; Tolppanen, Williams & Lawlor, 2011). For example, the NHANES study expressed no relationship between VitD concentration and neurocognitive functioning in adolescents and adults (McGrath et al., 2007). In a longitudinal study on Puerto Rican adults from the Boston Area, the basal serum 25(OH)D level was not associated with a 2-year change in cognitive test scores, executive function, and memory domains (Palacios, Scott, Sahasrabudhe, Gao & Tucker, 2020).

A double-blind controlled trial reported that VitD supplementation does not influence cognitive function and mood in healthy young adults. In these participants, despite significant increases in VitD consumption, no significant changes were observed in working memory (F=1.09; P=0.30), cognitive flexibility (F=1.37; P=0.24) and response inhibition (F=0.82; P=0.37) (Dean et al.,

Table 2. Effects of vitamin D supplementation on cognitive abilities, insomnia, and daytime sleepiness scores

Tests	Scores / Mean±SD		P	
	Baseline	After Supplementation		
Test of cognitive abilities (n=940)*	Memory	14.7±7.9	25.6±3.9	<0.001
	Inhibitory control and selective attention	16.3±6.1	18.7±4.1	<0.001
	Decision making	13.6±5.5	18.7±4.3	<0.001
	Planning	8.2±3.6	11.2±3.0	<0.001
	Sustained attention	8.6±3.1	9.9±3.1	<0.001
	Social cognition	9.5±3.3	10.1±3.6	0.091
	Cognitive flexibility	11.2±3.4	13.5±3.4	<0.001
	The total score of cognitive tasks	82.9±24.0	105.8±16.0	<0.001
Insomnia**	No insomnia (n=724)	0.11±0.10	0.10±0.11	0.667
	Some degree of insomnia (n=216)	9.2±5.1	5.7±6.3	<0.001
Daytime sleepiness**	No sleepiness (n=718)	0.06±0.1	0.06±0.09	0.991
	Some degree of sleepiness (n=222)	7.5±3.6	6.6±4.4	<0.001

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The paired-sample t-test; *Higher score represents a better function; **Lower score represents a better function.

2011). In another study, no treatment-induced improvement in cognition or behavior was observed in nursing home residents (Przybelski et al., 2008). In a randomized clinical trial among 422 subjects, no significant associations were found between serum 25(OH)D level and the three independent cognitive tasks (verbal recall test, coding test, and tapping test) at baseline. After four months, VitD supplementation did not promote cognition in mid-aged and older individuals (Jorde et al., 2019). The small sample size, the presence or absence of confounding variables, short intervention duration, and test reproducibility may preclude the observation of positive effects in these studies.

The improvement in sleep disorders is important because sleep disorders are associated with several health problems (Bagai, 2010; Goel, Rao, Durmer & Dinges, 2009; Skaer & Sclar, 2010). Although VitD is crucial to many physiologic processes in man, there are limited data in relation to its effects on sleep disorders. There is a wealth of evidence that VitD is involved in sleep regulation by decreasing prostaglandin D2 and cytokine (Feldman et al., 2007; Jablonski, Chonchol, Pierce, Walker & Seals, 2011; Krueger, Majde & Rector, 2011).

VitD deficiency may be contributed to the development of symptoms of wakefulness most frequently associated with sleep disorders (McCarty et al., 2012). Our study showed that high-dose VitD supplementation significantly reduced the severity of insomnia among adolescents. These findings are compatible with the study of Khoo et al., who reported that serum VitD levels in healthy individuals were inversely associated with sleep-regulating factors such as tumor necrosis factor-alpha and interleukin-1 (Khoo et al., 2011).

Our results are similar to those of Bellia et al., who reported that a low VitD status might contribute to sleepiness through central nervous system signaling and inflammatory mediators (Bellia et al., 2013). McCarty et al. have also announced that serum 25(OH)D concentrations are linked with ESS in patients with sleep disorders (McCarty et al., 2012). One possible mechanism for this inverse correlation may be the reduced levels of sympathetic stimulation or deactivation of the hypothalamic-pituitary-adrenal stress response axis. A recent systematic review and meta-analysis have reported that those with low vitamin D had a significantly higher risk of sleep disorders (OR:1.5; 95%CI: 1.3-1.7), poor sleep

Table 3. Effects of vitamin D supplementation on subjects with insomnia and daytime sleepiness

Subjects	No. (%)		P
	Baseline	After Supplementation	
Only insomnia	141 (15.0)	106 (11.3)	0.003
Only sleepiness	147 (15.6)	138 (14.7)	
Insomnia +sleepiness	75 (8.0)	57 (6.1)	
Normal	577 (61.4)	639 (67.9)	

*P-Value obtained from Cochran's Q test.

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quality (OR: 1.6; 95% CI: 1.2- 2.0), short sleep duration (OR: 1.7; 95% CI: 1.3- 2.3), and sleepiness (OR: 1.4; 95%CI: 1.1-1.6) (Gao et al., 2018).

The strong points of this study are its large number of carefully selected participants, comprehensive measures of the baseline characteristics, and its powerful assessment of cognitive abilities and detection of insomnia and sleepiness. To detect any possible beneficial effects of VitD supplementation on cognitive abilities and sleep disorders, characteristics of the study population, the dose of VitD, duration of intervention, and methods of cognitive testing are important. The given oral mega-doses effectively corrected severe VitD deficiency in peripheral blood, but it is still unclear whether normalization of impaired plasma level of VitD reflects the status of VitD in the Cerebrospinal Fluid (CSF) and cells in CNS.

Our study has several limitations. Our participants consisted of healthy adolescent girls who were free of cognitive impairment and major psychiatric illness. Therefore, our findings may not be generalized to clinical patients demonstrating emotional disorders or cognitive impairment. Because all observations received supplementation in the main study, we could not use a control group for comparison.

5. Conclusion

Our findings reveal that VitD supplementation improves cognitive abilities and sleep problems in healthy adolescents with a high prevalence of VitD insufficiency and deficiency. This approach may be a valuable means of improving cognitive abilities and sleep problems. Besides, treating VitD deficiency may benefit the general population other than the teenagers if other larger studies confirmed similar effects on different age and ethnic groups. Although detection and treatment of VitD deficiency are crucial for a range of health outcomes, future randomized controlled trials in key populations of

interest are needed to clarify the causal contribution of VitD status to brain-related effects and elucidate whether supplementation can improve abilities in these domains.

Ethical Considerations

Compliance with ethical guidelines

All procedures were performed following the ethical standards of the Institutional and or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all study participants.

Funding

This study was supported by grants No. 931188 (Majid Ghayour-Mobarhan) from Mashhad University of Medical Sciences.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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