Review Paper

Magnesium Status and Supplementation in Children With Attention-deficit/Hyperactivity Disorder: A Systematic Review

Parinaz Kalejahi[1*], Seyed Gholamreza Noorazar[1]

1. Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition that can have major effects on the affected individual's personal and social life. Complementary treatments, including nutritional supplements, can help improve the symptoms of patients with ADHD. Therefore, this review study investigated magnesium deficiency in children with ADHD and the effectiveness of this mineral supplement.

Methods: This paper systematically reviewed the literature available in Google Scholar, PubMed, and Scopus databases. Studies focusing on children with ADHD published in English were selected without any time limitations, up to December 2023. From a comprehensive review of 1,115 publications, eight articles were carefully selected for inclusion in the study.

Results: Selected descriptive studies have demonstrated a correlation between ADHD and reduced levels of magnesium in children's serum and hair compared to their healthy counterparts. Furthermore, magnesium supplementation is an effective means of mitigating the symptoms associated with this disorder.

Conclusions: According to recent research, magnesium micronutrient has shown potential in alleviating the symptoms associated with ADHD. This is attributed to its pivotal role in the central nervous system. Given its significance in regulating neurotransmitters and synaptic plasticity, magnesium is a valuable addition to the existing treatment options for ADHD. Further studies are warranted to fully elucidate its efficacy and potential side effects. Nonetheless, the findings thus far are promising and merit consideration by healthcare professionals.

** Corresponding Author:*
Parinaz Kalejahi, PhD.
Address: *Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.*
E-mail: *parinaz.kalejahi@gmail.com*

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition marked by challenges in attention, impulsiveness, hyperactivity, and emotional regulation [1]. These deficits can lead to impairments in various areas of life, and many children continue to exhibit significant symptoms even as they grow into adolescence and adulthood [2]. The global incidence of ADHD is estimated to be around 5-7% in children and adolescents, and around 2.5% among adults [3, 4].

The origin of this disorder is still unknown, but it seems that genetic and environmental factors are involved in its development [5]. Environmental factors, such as nutritional factors and diet patterns, have been demonstrated to significantly contribute to the development of ADHD symptoms. As a result, there is a growing interest in using nutritional approaches to help manage ADHD. Scientific research in this area is increasing, and it is hoped that this will lead to new insights and treatment options for individuals with ADHD [6, 7].

Research in this area suggests that children with this disorder may have lower levels of important minerals, like magnesium, compared to healthy children [8, 9]. However, supplementing these nutrients has been shown to have a positive impact on managing the symptoms of the disorder [9, 10]. Magnesium is a critical cation in the central nervous system that plays a crucial role in various functions, including signal transmission and intracellular signaling [9].

Magnesium, in turn, plays a crucial role as a voltage-gated antagonist to the glutamate, N-methyl-D-aspartate (NMDA) receptor and also functions as an antagonist to calcium entry through voltage-gated channels of all types. It is worth noting that while magnesium levels in the brain tend to be more stable and decrease more gradually than in other tissues, even small reductions can have a profound effect on neuronal functioning [11].

Magnesium has been found to have a direct impact on dopamine release and the stimulatory effect of glutamate on dopamine release at the presynaptic level [12-14]. Low levels of magnesium may increase glutamatergic neurotransmission, potentially fostering an environment that promotes excitotoxicity. This may cause oxidative stress and neuronal loss [15]. Despite magnesium's critical role in the central nervous system, there is limited research on its effects on ADHD [16]. Also, magnesium deficiency is linked to behavioral symptoms, such as anxiety and irritability, which can lead to a worsening of ADHD symptoms. Some studies have shown that magnesium supplements may be effective in improving some mental and neurological conditions, which could be explored as a treatment option for ADHD. Therefore, this systematic review aimed to evaluate existing research on the serum levels of magnesium in children with ADHD, as well as clinical trials on magnesium supplementation in these children.

Methods

Review design

This study was conducted adhering to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocol.

Articles published until December 2023 were retrieved through a search in PUBMED/Medline, Google Scholar, and Scopus databases. Unpublished studies and documents were also manually searched and reviewed. Correspondence was also conducted with the corresponding author if the findings of an article were not available.

Search strategy

Keywords used to search for articles were in accordance with the MeSH glossary. Free keywords were also used in addition to MeSH keywords to search for articles. The following keywords were used alone or cross-linked, depending on which database was searched:

(Attention deficit disorder with hyperactivity [MeSH terms]) OR (ADHD [Title/Abstract]) OR (deficit-hyperactivity disorders, attention [Title/Abstract]) OR (hyperkinetic syndrome [Title/Abstract]) OR (attention deficit disorder [Title/Abstract]) AND (magnesium [Title/Abstract]) OR (mg [Title/Abstract])

Inclusion and exclusion criteria

Inclusion criteria based on the PICOS framework (population/intervention/comparators/outcomes/time/setting) were as follows:

Population: Studies on children with ADHD published in English;

Intervention: Supplementation with magnesium and, for descriptive studies, assessment of magnesium in serum, urine, or hair;

Outcome: Improvement in ADHD symptoms in the clinical trial;

Time/date: Publication date up to December 2023 without any location restrictions.

The exclusion criteria were as follows:

1) Reviews, systematic reviews, or meta-analyses, 2) Not enough information, 3) Studies in languages other than English or Persian, 4) Incomplete articles or obscure statistical results.

Data selection and extraction

We imported publication titles and abstracts into ENDNOTE, version 7 and removed duplicates. Two independent reviewers screened and evaluated all publications. We first screened article titles and abstracts and then reviewed full publications based on pre-specified criteria.

The selected studies were entered into Excel software. The data form was designed as follows: Published information included the author's name, year of publication, country, type of intervention, type of magnesium measurement, final sample size, participants, possible side effects, and final results.

Quality assessment

The risk of bias in the included studies was assessed using the National Institutes of Health (NIH) quality assessment tool and Cochrane collaboration tool (Tables 1 and 2).

The NIH quality assessment tool for assessing bias in cross-sectional studies was used, which includes the following subscales: Study population, participation rate, recruitment criteria, sample size justification, exposure(s) of interest measured prior, sufficient time frame to observe the effect, different levels of exposure, exposure measures and assessment, repeated exposure measurement, outcome measures, outcome assessors blinded, and follow-up rate.

To evaluate the quality of intervention articles, the Cochrane tool was employed, which has seven subscales: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective bias, and other sources of bias.

Results

Study selection

We found 1115 articles and, after removing duplicates, 917 articles were selected for the next step. After reviewing the studies by two separate researchers, 63 studies were selected, and finally, 8 studies were selected to be included in the review study (Figure 1).

Study characteristics

Out of the studies that were selected, 5 were clinical trials [10, 17-20] and 3 were descriptive studies that compared the serum magnesium as well as magnesium concentrations in the hair of children diagnosed with ADHD with those of healthy children [8, 21, 22]. In three clinical trial studies, magnesium supplementation was given as a single therapy [10, 17], while in the remaining 3 studies, magnesium was supplemented along with other nutrients, such as vitamin D, zinc, calcium, and omega-3 [18-20]. The duration of the intervention, as reported in the studies, was either 8 or 12 weeks. The total number of people was 1285, and the studies were conducted from 2010 to 2021 in the following countries: Iran (3 studies) [17-19], Egypt (2 studies) [10, 22], Germany (1 study) [20], Russia (1 study) [23], and India (1 study) [21]. Tables 3 and 4 show the characteristics and results of the selected studies.

Assessment of magnesium concentrations in the serum and hair of children diagnosed with ADHD

In Mahmoud et al.'s study, 58 hyperactive children and 25 healthy children in the age range of 5-15 years were selected. Serum levels of magnesium were lower in hyperactive children compared to healthy children, and ferritin and zinc levels were also reported to be lower in these children [22].

In the next study conducted by Moghaddam et al., 148 children in the age group of 4-9 years were studied, and ADHD and autism spectrum disorder (ASD) children were compared with the healthy group. The levels of magnesium in the hair in ADHD and ASD children were lower than in healthy children, but the serum levels of magnesium in the groups [23]. In Varahala et al.'s study, 100 ADHD and healthy children aged 6-17 were studied, and ADHD children had lower serum magnesium levels compared to healthy children [21].

Table 1. Risk of bias for the selected cross-sectional studies: NIH quality aqssessment tool

Author(s), Year	Research Question	Study Population	Participation Rate	Recruitment Criteria	Sample Size Justification	Exposure(s) of Interest Measured Prior	Sufficient Time Frame to See Effect	Different Levels of Exposure	Exposure Measures and Assessment	Repeated Exposure Measurement	Outcome Measures	Outcome Assessors Blinded	Follow-up Rate	Statistical Analyses
Mahmoud et al. 2011 [22]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	N	Y
Skalny et al. 2019 [23]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y
Varahala et al. 2020 [21]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	N	Y

Y: Yes, N: No.

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Effect of magnesium supplementation on ADHD children

Five interventional studies were included in this review:

In El Baza et al.'s study, a total of 50 hyperactive children aged 6-16 years were supplemented with magnesium (200 mg/day as an adjunctive treatment to the standard medical treatment) or a placebo for 8 weeks, and after 8 weeks, significant improvement was seen in the children's cognitive function [10].

In Huss et al.'s study, 810 children aged 5-12 years were supplemented with omega-3 and omega-6, zinc, and magnesium (80 mg/day) for 12 weeks, and the result showed an improvement in attentional, behavioral, and emotional problems of children [20].

In a 2020 study by Hemamy et al., 66 children with ADHD were supplemented with vitamin D (50,000 IU/week) and magnesium (6 mg/kg/day) for 8 weeks. After 8 weeks of taking both vitamin D and magnesium, the intervention group experienced a significant increase in serum levels of 25-hydroxy vitamin D3 and magnesium compared to the placebo group. This supplementation also resulted in a marked reduction in conduct and social difficulties [19].

Table 2. Risk of bias for the selected clinical trials: The Cochrane collaboration tool

Author(s), Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
El Baza et al. 2015 [10]	+	?	?	?	-	?	+/-
Huss et al. 2010 [20]	+	-	?	?	-	?	?
Hemamy et al. 2020 [19]	+	+	+	+	+/-	+/-	+/-
Noorazar et al. 2021 [17]	+	+	+	+	-	?	-
Moghaddam et al. 2016 [18]	+	+	+	+	-	?	?

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Table 3. Studies on magnesium levels in ADHD children

Author, Year	Sample	Study Type	Psycho-pathological Scale	Results	Direction of Evidence
Mahmoud et al. 2011 [22]	58 children aged 5-15 years	Observa-tional	DSM-IV	Children with ADHD had notably lower levels of zinc, ferritin, and magnesium compared to the control group (P=0.04, 0.03, and 0.02, respectively)	(+)
Skalny et al. 2019 [23]	148 boys aged 4–9 years were enrolled in this study, including 44 children with ADHD, 40 pediatric patients with ASD, 32 patients with both ADHD and ASD, as well as 32 healthy neurotypical children	Case-control	ICD-10	Magnesium levels in hair were lower in children with ADHD and those with both ADHD and ASD compared to healthy con-trols. However, there were no significant differences in serum magnesium levels between the groups. Additionally, children with both ADHD and ASD showed higher urinary magnesium levels than the control group.	(±)
Varahala et al. 2020 [21]	50 cases of ADHD from the outpatient department of the psychiatry clinic for children and adolescents and also 50 controls aged 6-17 years were selected.	Case-control	DSM-V	In the ADHD group, 24% of children had serum magnesium levels below 1.5 mEq/L, whereas only 6% of children in the control group had levels this low. Upon further analysis of subgroups, 25% of children with hyperactive ADHD, 18.75% with inattentive ADHD, and 27.27% with combined ADHD showed serum magne-sium concentrations under 1.5 mEq/L.	(+)

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Abbreviations: ADHD: Attention-deficit/hyperactivity disorder; DSM: Diagnostic and statistical manual of mental disorders; ICD-10: International statistical classification of diseases and related health problems-10th revision.

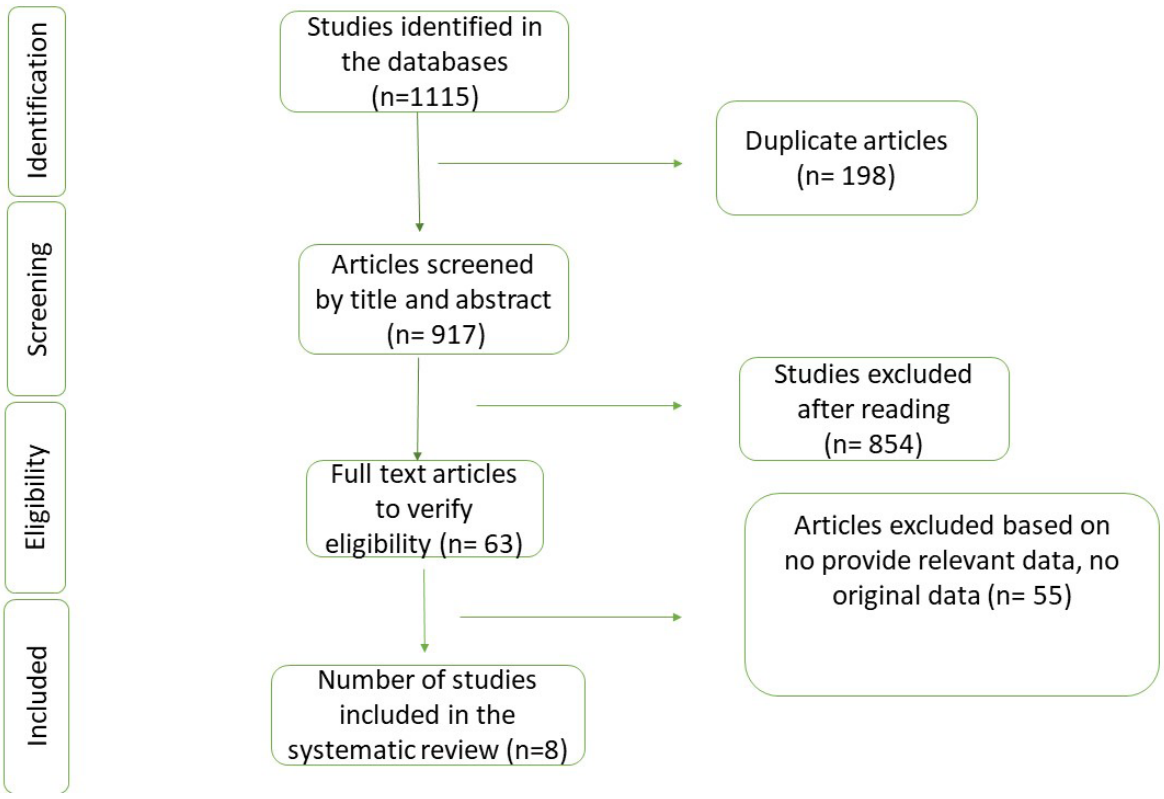

Figure 1. Flow diagram of the study selection

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Table 4. Clinical details of all included studies investigating the effect of magnesium as treatment

Author, Year	Sample	Study Type	Psycho-pathological Scale	Treatment	Treatment Duration	Results	Direction of Evidence
El Baza et al. 2015 [10]	25 patients with ADHD and 25 controls receiving a placebo, aged between 6 and 16 years	Randomized controlled clinical trial	DSM (IV), Conners' parent rating scale, Wisconsin's card sorting test (WCST)	The administration of a 200 mg/day dose was used as an adjunct treatment to conventional medical therapy.	8 weeks	Magnesium deficiency was identified in 18 children with ADHD, accounting for 72% of the group. Those who received magnesium supplements showed improvements in cognitive functions, as evaluated by the WCST and Conners' rating scale. The patients experienced only mild side effects from the magnesium supplementation.	(+)
Huss et al. 2010 [20]	810 children aged 5 to 12 years	Clinical trial	SNAP-IV Rating Scale	Omega-3 EPA (400 mg)+ Omega-3 DHA (40 mg)+ Omega-6 GLA (60 mg)+ Magnesium (80 mg) + zinc (5 mg)	12 weeks	The combination of omega-3 and omega-6 fatty acids plus magnesium and zinc caused positive effects on attentional, behavioral, and emotional challenges in youth, while presenting few side effects.	(+)
Hemamy et al. 2020 [19]	66 children with ADHD aged between 6 and 12 years	Double-blind, randomized controlled clinical trial	DSM IV Conners' parent rating scale48 (CPRS48)	The intervention included 50,000 IU of vitamin D per week and magnesium supplements (6 mg/kg/day) or placebo treatments.	8 weeks	Following 8 weeks of supplementation with vitamin D and magnesium, the intervention group showed a significant rise in serum levels of 25-hydroxy vitamin D3 and magnesium compared to the placebo group. This combined supplementation also led to a notable reduction in conduct and social problems.	(+)
Noorazar et al. 2021 [17]	40 children with ADHD aged 7-12 years old	Double-blind, randomized controlled clinical trial	Conner's parent rating scale	The intervention group received treatment with methylphenidate (0.5–1 mg/kg/day) combined with 10 mg of magnesium, while the control group was given methylphenidate (0.5–1 mg/kg/day) along with a placebo	8 weeks	At baseline, the average total score was 74.4±10.4 for the intervention group and 76.8±6.6 for the control group (P=0.79). After the intervention, the Conner's parent rating scale total score decreased to 61.9±11.1 in the intervention group and 68.8±7.3 in the control group (P=0.02). Additionally, there was a significant difference between the groups in the inattention subscale scores (P=0.001).	(+)

Author, Year	Sample	Study Type	Psycho-pathological Scale	Treatment	Treatment Duration	Results	Direction of Evidence
Moghaddam et al. 2016 [18]	40 patients with ADHD aged 6 to 12 years	Double-blind, randomized controlled clinical trial	ADHD rating scale	The patients were randomly assigned to two groups. The treatment group received methylphenidate twice daily, starting at a dose of 0.3 mg/kg, which was gradually increased to 1 mg/kg over two weeks. In addition, this group was given tablets containing 133 mg of zinc, 333 mg of calcium, and 5 mg of magnesium. Meanwhile, the control group was administered the same methylphenidate dosage along with a placebo.	8 weeks	The average symptom severity score in the case group was 40.4±2.4 prior to treatment and decreased to 19.5±6.1 following 8 weeks of treatment (P<0.001).	(+)

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In a 2021 study by Noorazar et al., 40 children received magnesium supplementation (10 mg/day) for 8 weeks. After 8 weeks, a significant decrease was observed in the total score of the Conner's test and the inattention score in the intervention group [17].

Moghaddam et al. in 2016, 40 ADHD children were supplemented with zinc, magnesium (5 mg/day), and calcium for 8 weeks, and after the intervention, a significant reduction was observed in the severity of hyperactivity symptoms [18].

Discussion

In the selected descriptive studies, it was observed that children diagnosed with ADHD displayed lower serum and hair levels of magnesium, while urinary magnesium levels were comparatively elevated in comparison to their healthy counterparts [8, 22, 23]. These findings suggest an altered magnesium status in ADHD-afflicted individuals. Clinical trial studies indicate that magnesium supplementation for 8 to 12 weeks can mitigate clinical symptoms of ADHD while also reducing other associated symptoms, such as anxiety and social problems in affected children [10, 17-19].

The pivotal role of magnesium in the pathway of neurotransmitter function is of great significance in ADHD. The intricate interaction of magnesium with neurotransmitters is fundamental in regulating signal transmission, which, in turn, plays a vital role in the cognitive and behavioral functioning of individuals [11, 24, 25].

Magnesium's interaction with the NMDA receptor (NMDAR) is one of its key neurological functions. The malfunctioning of the NMDAR can lead to complex alterations in the levels of neurotransmitters, such as dopamine and epinephrine in the brain, which can significantly contribute to the manifestation of ADHD symptoms [26, 27]. It is noteworthy that the primary pharmacotherapeutic agents employed in the treatment of ADHD, methylphenidate and atomoxetine, have been demonstrated to regulate the function of NMDARs, which are essential for learning and memory processes. Furthermore, clinical trials have shown that pharmacological agents that directly target NMDARs, such as memantine and amantadine, exhibit efficacy in ameliorating the symptoms of ADHD. These findings suggest that NMDAR function may be a critical target for the development of novel pharmacotherapeutic agents for ADHD [28-30].

Magnesium has been identified as a regulator of presynaptic glutamate release, and its effects on glutamate neurotransmission have been linked to the pathophysiology of ADHD. Research has shown that an increase in glutamatergic activity in the frontal and striatal brain regions, as well as elevated levels of glutamate in the anterior cingulate cortex, may be associated with ADHD. Therefore, the regulatory effects of magnesium on glutamate neurotransmission can be regarded as another therapeutic intervention for this disorder [15].

Another effect of magnesium can be related to the brain-derived neurotrophic factor (BDNF) mechanism [31]. Research suggests that decreased levels of BDNF may play a role in the neurodevelopmental deficits

observed in individuals with ADHD. Moreover, it is believed that this deficiency may also contribute to the persistence of the disorder into adulthood. In this field, studies have shown that magnesium can increase the levels of this neurotrophin. The role of magnesium as a calcium antagonist and voltage-dependent blocker of the NMDA channel may be connected to its effect on BDNF [32, 33].

Magnesium can also play a role in the dopamine neurotransmitter pathways [34]. Studies conducted on animals have demonstrated that magnesium is capable of activating tyrosine hydroxylase (TH) [35]. TH is a key enzyme that plays a vital role in the biosynthesis of several important neurotransmitters, such as dopamine, norepinephrine, and epinephrine. It converts the amino acid tyrosine into L-DOPA, which is a precursor for the formation of these neurotransmitters. This conversion is considered to be the rate-limiting step in the biosynthesis of catecholamines. Without the activity of TH, the production of these neurotransmitters would be severely impaired [13]. In addition, magnesium has a fascinating impact on the generation of cyclic adenosine monophosphate response element binding protein (CREB) within the brain. This protein plays a crucial role in regulating the activity of genes that influence the functioning of the human brain, particularly those involved in dopamine production. By binding to specific DNA sequences known as cAMP response elements (CREs), CREB can either enhance or diminish gene transcription. It has been found that children with ADHD who suffer from magnesium deficiency may experience adverse effects on their health, and magnesium supplementation can have a positive impact on these children. The available findings strongly support the hypothesis that magnesium supplementation can help alleviate the symptoms of ADHD in affected children [26].

Conclusion

Magnesium may play a significant role in managing ADHD symptoms. Individuals with ADHD often have lower serum magnesium levels, and magnesium supplementation can lead to improvements in hyperactivity, impulsivity, and attention deficits. Magnesium is crucial for neurotransmitter function, which may explain its potential benefits in ADHD management.

However, the evidence is mixed, and more extensive, high-quality research is needed to confirm these findings and establish optimal supplementation guidelines.

Limitations

This study also had limitations. Some studies had small sample sizes, limiting the generalizability of their findings. Also, studies often do not account for factors, like concurrent medications or comorbidities, that could influence results. In addition, different methods for measuring magnesium levels (serum, hair, and urine) can lead to inconsistent results.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (Code: TBZMED.REC 139).

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Authors contributions

Conceptualization: Parinaz Kalejahi, Supervision, data collection, funding acquisition and resources: Gholamreza Noorazar; Methodology, investigation and writing: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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