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## *Effect of Magnesium Supplementation on Children with Attention Deficit Hyperactivity Disorder (ADHD)*

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### ABSTRACT

**Background:** Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children and youths. The prevalence of this disorder was reported between 5-10% in literature. Children with ADHD are characterized by hyperactivity, lack of attention, and impulsivity. The aim of this review was to overview the role of magnesium supplementation in the treatment of ADHD. **Methods:** Data bases including PubMed, Scopus, Sciencedirect, Web of science, and Google scholar were searched by using these keywords: Attention deficit hyperactivity disorder, ADHD, and Magnesium. The related observational and interventional studies published up to February 2017 were extracted and used. **Results:** Recent studies suggest that ADHD symptoms may have contribution in nutrients' status in body, such as magnesium. While most of these studies suggest a low magnesium level in children with ADHD, there have not been enough well-designed controlled clinical trials to demonstrate the efficacy and safety of magnesium supplementation or dietary magnesium interventions as a treatment. **Conclusions:** Considering the contradictory findings about the magnesium and ADHD, magnesium therapy in children with ADHD is not recommended until enough well-designed studies are provided.

**Keywords:** Attention deficit hyperactivity disorder; Magnesium; Supplementation; Treatment

### Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children and youths. The prevalence of this disorder is almost 5% (Faraone and Doyle, 2001) and can increase even up to 10% (Rowland *et al.*, 2002). Children with ADHD are symptomatologically characterized by hyperactivity,

lack of attention, and impulsivity (Biederman *et al.*, 1991). The clinical presentation of ADHD depends on gender, disruptive behaviors, and comorbid disorders, which are more common in boys than girls (Biederman *et al.*, 2002). Although evidences indicate that ADHD is a highly genetic disease, environmental risk factors also have been reported

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as effective. Chemical exposures, prenatal substance exposures, lifestyle, psychosocial, and nutritional factors are some of these risk factors (Goldstein, 2009). Based on the recent investigations, nutrients can be important in the expression and treatment of ADHD. In addition, some studies suggest that ADHD symptoms may have contribution in nutrient levels (Arnold *et al.*, 2011, Milte *et al.*, 2012, Nigg *et al.*, 2012). Some of these nutrients include zinc, iron, vitamin D, and magnesium (Villagomez and Ramtekkar, 2014).

Magnesium is an essential factor for all the living organisms. Regular intake of magnesium is essential for humans to prevent from its deficiency. Regarding the magnesium's various functions within the human body, it is necessary to prevent and treat various diseases. Decreased magnesium levels are in association with chronic diseases, such as asthma, ADHD, type 2 diabetes mellitus, insulin resistance, hypertension, Alzheimer's disease, osteoporosis, and cardiovascular disease (e.g., stroke) (Song *et al.*, 2005).

The function of almost 325 enzymes is relevant to magnesium (Eby and Eby, 2010). In mouse samples, magnesium affects the dopaminergic, serotonergic, and noradrenergic receptors (Cardoso *et al.*, 2009). The effect of dopaminergic and noradrenergic receptors on etiology of ADHD has been recently studied (Del Campo *et al.*, 2011, Wu *et al.*, 2012). There are contradictory evidences about the magnesium and ADHD pathophysiology, ADHD-involved neurotransmitters and stimulants effect on magnesium status in ADHD children and youths, as well as safety recommendations. So, investigating the effect of magnesium in handling ADHD is highly required (Archana *et al.*, 2012, Irmisch *et al.*, 2011, Mahmoud *et al.*, 2011, Nogovitsina and Levitina, 2007). The aim of this review is to overview the role of magnesium supplementation in treatment of ADHD.

### Materials and Methods

The related articles published up to February 2017 were extracted through searching electronic databases of PubMed, Scopus, Sciencedirect, Web of science, and Google scholar. The search

was conducted without any constraints. The following keywords were used: Attention deficit hyperactivity disorder, ADHD, and Magnesium. English abstracts of non-English language articles were provided so that their results can be used in the study. Observational studies and interventional studies (clinical trials) were extracted and included in the research.

### Results

A total number of 116 articles were screened, 6 of them were duplicated and 103 of them were irrelevant. Generally, interventions by administering magnesium supplements were reported in seven articles (El Baza *et al.*, 2016, Huss *et al.*, 2010, Mousain-Bosc *et al.*, 2006, Mousain-Bosc *et al.*, 2004, Nogovitsina and Levitina, 2006a, Starobrat-Hermelin, 1998, Starobrat-Hermelin and Kozielec, 1997). Only one magnesium monotherapy study was found (El Baza *et al.*, 2016) and two articles were not in English (Nogovitsina and Levitina, 2006a, Starobrat-Hermelin, 1998). Therefore, the studies including multinutrient formulas with magnesium were reviewed.

A clinical examination of 122 children aged 6-11 years among senior schoolchildren in Nefteyugansk, Russia in 2006 showed a low serum magnesium level in these children. Furthermore, magnesium levels in erythrocytes and Mg (2+)-ATPase activity were decreased significantly (Nogovitsina and Levitina, 2006b). In 2009, a case-control study compared 20 children with ADHD with 20 healthy children aged 5-12 years old. Protein thiols and pseudocholinesterase as well as ceruloplasmin and magnesium levels were measured in saliva as antioxidant indicators. Protein thiols and Pseudocholinesterase levels increased while ceruloplasmin levels did not change significantly. A significant low salivary magnesium was observed (Archana *et al.*, 2012). In another case-control study on 58 children with ADHD (in three subgroups: 32 children with inattentive type/10 children with hyperactive type/16 children with combined type) and 25 healthy controls in 2011, it was revealed that zinc, ferritin, and magnesium levels were lower than normal in children with ADHD while copper levels

were normal. Zinc in all subgroups, ferritin in both inattentive and hyperactive subgroups, and magnesium in both hyperactive and combined subgroups were subnormal (Mahmoud *et al.*, 2011).

Despite the findings of mentioned studies, two studies indicated an elevated serum magnesium level in children with ADHD. The first investigation was a case-control study conducted on 35 children with ADHD compared with 112 healthy controls in two phases. The frequency and severity of skin/thirst symptoms in phase 1 and biological evidence of eicosapentaenoic acid (EFA) insufficiency in phase 2 were evaluated. Serum ferritin, magnesium, and ascorbate levels were higher in children with ADHD, but iron, zinc, and vitamin B6 status were not different significantly (Antalis *et al.*, 2006). The second case-control study was carried out on 9 children with ADHD versus 11 healthy participants. In this study serum lipid profile, lipoproteins, and magnesium were evaluated. The serum magnesium and HDL were elevated while Apo B levels were reduced (Irmisch *et al.*, 2011).

The effect of magnesium supplementation on ADHD symptoms: in a controlled clinical trial study, a group of 50 children were selected; 25 participants received standard treatment and magnesium supplementation, while the other half received only standard treatment. All the participants with ADHD were magnesium deficient. In this trial, standard treatment along with magnesium supplementation resulted to a decline in hyperactivity; on the contrary, standard treatment alone resulted to an increase in hyperactivity (Starobrat-Hermelin and Kozielc, 1997).

In another study a formula consisting of poly unsaturated fatty acids (PUFA) in combination with zinc and magnesium was used. In this regard, 810 children with ADHD in the age range of 5-12 years were investigated for three months to evaluate the effect of supplementation on ADHD symptoms. Both inattentiveness and hyperactivity/impulsivity decreased significantly during the study (Huss *et al.*, 2010).

An open label study was conducted on 52 children with ADHD aged 0 to 17 years. In this trial, magnesium at a dose of 6 mg/kg/day for a period of

one to six months was prescribed. After taking the regimen, intraerythrocyte magnesium level reached normal level during two months but scholar inattention decreased during four months in almost 57% of children (Mousain-Bosc *et al.*, 2004).

Another open label study on 76 children with ADHD (intervention: 40/ control: 36) showed a significant reduction in hyperactivity and inattentiveness along with increase in the serum magnesium level after following a Magnesium-vitamin B6 regimen (6 mg/kg/day magnesium, 0.6 mg/kg/d vitamin B6) for 8 weeks (Mousain-Bosc *et al.*, 2006).

Nogovitsina *et al.* prescribed a polyvitamin complex including vitamin B6 and magnesium in a group of 31 children with ADHD aged 6-12 years and 20 matched children as the control group for 30 days. The supplementation caused improvements in children's behavior such as decrease in the level of anxiety, aggression, synkinesis, and inattention. Moreover, magnesium homeostasis has significantly improved (Nogovitsina and Levitina, 2006a).

El baza *et al.*'s study was a case-control prospective interventional comparative study which consisted of 25 children with ADHD and 25 age and gender matched healthy controls. The levels of magnesium in serum and hair were measured in all participants. It was reported that 72% (18) of ADHD children were Magnesium deficient. The magnesium deficient children were randomly allocated into 2 equal groups. The first group received magnesium supplementation in a dose of 200 mg/day along with standard medical treatment. The second group only received standard medical treatment. After 8 weeks, the treated ADHD cases who had low hair magnesium level demonstrated a significant improvement in hyperactivity, impulsivity, inattention, opposition, and conceptual level. On the contrary, the untreated low hair Magnesium ADHD cases showed no such improvement. The safety of magnesium supplementation was also proved (El Baza *et al.*, 2016).

## Discussion

Magnesium has important role in physiological and biochemical central processes (Bac *et al.*,

1998). It can affect catecholamine signaling in the brain and  $Mg^{2+}$  can control the glutamate N-methyl-aspartate channel that is also effective on excitotoxic cell death and apoptosis (Feillet-Coudray *et al.*, 2004, Schmidt and Taylor, 1988).

Some studies showed decrease in level of magnesium among children and youths with ADHD (Archana *et al.*, 2012, Mahmoud *et al.*, 2011, Nogovitsina and Levitina, 2006b). These studies reported that magnesium levels were significantly lower in both children with hyperactive than in controls. This may be due to the importance of magnesium in protecting cell membranes from excitatory neurotransmitters such as glutamate.

However, the reported associations were conflicting. Several studies observed increased level of magnesium in children with ADHD (Antalis *et al.*, 2006, Irmisch *et al.*, 2011).

Few studies also evaluated the effect of magnesium oral intake on severity of ADHD symptoms. In a controlled clinical trial study, Starobrat-hermelin *et al.* reported that all the participants diagnosed with ADHD were magnesium deficient. In this trial, standard treatment along with magnesium supplementation resulted in a decline of hyperactivity; on the contrary, standard treatment alone resulted to an increase in hyperactivity (Starobrat-Hermelin and Kozielc, 1997).

Huss *et al.* reported that the formula which consisted of poly unsaturated fatty acids (PUFA) in combination with zinc and magnesium decreased inattentiveness and hyperactivity/impulsivity in ADHD children, significantly (Huss *et al.*, 2010). Mousain *et al.* showed that magnesium/vitamin B6 intake decreased central nervous system hyper-excitability in ADHD children (Mousain-Bosc *et al.*, 2006). Nogovitsina *et al.* reported that a polyvitamin complex included vitamin B6 and magnesium caused improvements in the children's behavior such as decreasing the level of anxiety, aggression, synkinesis, and inattention, while improving magnesium homeostasis (Nogovitsina and Levitina, 2006b). El baza *et al.* showed that

magnesium supplementation in a dose of 200 mg/day along with standard medical treatment improved hyperactivity, impulsivity, inattention, opposition, and conceptual level in ADHD (El Baza *et al.*, 2016).

### Conclusions

While most of observational studies suggested a low magnesium level in children with ADHD, there have not been enough well-designed controlled clinical trials. This demonstrates the efficacy and safety of magnesium supplementation or dietary magnesium interventions for treating ADHD. These few interventional studies have several weaknesses in methodology such a small sample size and lack of masking. Moreover, magnesium was prescribed in combination with other nutrients in most of these studies (Huss *et al.*, 2010, Mousain-Bosc *et al.*, 2006, Mousain-Bosc *et al.*, 2004, Nogovitsina and Levitina, 2006a, Starobrat-Hermelin and Kozielc, 1997). Thus, it is not possible to evaluate the effect of magnesium on ADHD symptoms apart from the rest nutrients. Regarding a few evidences on therapeutic effect of magnesium on ADHD symptoms, magnesium therapy in children with ADHD is not recommended. Initially, enough double-blind randomized controlled clinical trials with larger sample size should be conducted and safety of magnesium supplementation is required to be proven.

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### Authors' contributions

Askari G. designed the work. Hemamy M., Mohammad Parast V., and Askari G. wrote the manuscript. Askari G., revised the manuscript and all authors approved the final version of the manuscript. There is also a consensus among authors for all aspects of the work.

### Conflicts of interest

The authors declare no conflict of interest.



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