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Magnesium as a potential complementary treatment for ADHD - a review of recent literature

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a relatively common neurodevelopmental mental disorder affecting an estimated 7.2% of children and adolescents, and 2.5% of adults. It manifests primarily through inattention, impulsivity, and hyperactivity. Multimodal treatment approaches are recommended, addressing the psychological, behavioral, vocational, and educational needs of patients and their families. Conventional therapies include pharmacologic interventions (e.g., psychostimulants) and non-pharmacologic strategies (e.g., psychotherapy, cognitive-behavioral therapy). The ongoing search for novel treatment options focuses on improving cognitive function, psychological well-being, and ADHD symptomatology. Nutritional interventions with vitamins and minerals are emerging as potential complementary or adjunctive therapies.

This review summarizes recent literature (past 5 years) on the relationship between magnesium and ADHD, encompassing observational studies, interventional trials, and meta-analyses. Evidence from recent publications suggests that children with ADHD have reduced magnesium levels and that magnesium supplementation improves symptoms. However, these studies do not definitively establish the exact cause-and-effect relationship between magnesium and ADHD. Current data are insufficient to recommend magnesium for routine ADHD treatment. High-quality, large-scale, and long-term studies are necessary to definitively understand the magnesium-ADHD link and to evaluate the effectiveness and safety of magnesium supplementation as an adjunct therapy. These studies should define optimal doses, forms, and duration of supplementation for safe and effective clinical use.

Key words: Attention Deficit-Hyperactivity Disorder; ADHD; Magnesium;

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD)

ADHD is a relatively common neurodevelopmental disorder that occurs in both children and adults[1]. The prevalence of ADHD diagnoses has risen in recent decades and is estimated to affect 7.2% of children and adolescents and 2.5% of adults[2]. While the male-to-female ratio in children is often reported to be 4:1, it approaches 1:1 in adults[3]

Definition and Symptoms

ADHD is characterized by three core symptoms: inattention, impulsivity and hyperactivity[4]. Symptoms typically emerge in childhood and persist into adolescence and adulthood in up to 90% of cases[5,6]. Diagnostics classification systems such as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the International Classification of Diseases, 10th and 11th editions (ICD-10/11) define ADHD according to behavioral criteria based on observation and informant reports. Unfortunately, there is a great heterogeneity of symptoms, which may be challenging. Symptoms can vary in presentation, coexist with other conditions, fluctuate based on context, and may not always be readily apparent during clinical evaluation.

Additionally, the course of ADHD is variable, with individuals experiencing different symptoms with varying degrees of severity throughout their lives. Moreover, there is a lack of valid neurobiological markers or other objective criteria that could lead to a clear diagnostic classification. The current understanding of this disorder encompasses a broader and more heterogeneous spectrum of presentations[7,8].

Etiology

The etiology of ADHD remains unclear. It is suspected to be multifactorial[9]. Numerous publications explore the influence of genetic[10–14], environmental[15], maternal[16–18], prenatal[19,20] and perinatal factors[21–23].

Impact of ADHD

ADHD has a significant impact on various areas of life. It is commonly diagnosed in children with learning difficulties, social dysfunctions and consequently, low academic and social development[5,24,25]. Patients often experience low self-esteem and emotion regulation difficulties. Additionally, ADHD is a risk factor for defiant and destructive behavior, self-harm, and substance abuse[26]. Comorbidity with other mental disorders is frequent, for example autism spectrum disorder (ASD) commonly observed in children and bipolar disorder in adults with ADHD[27–29]. Studies also suggest links between ADHD and both gaming disorder[30] and internet addiction[31] in adolescents and young adults. Furthermore, childhood ADHD is associated with an increased risk of alcohol use disorders in adulthood. Regarding tobacco use, smokers with childhood ADHD smoke significantly more cigarettes during adolescence than those without ADHD[2]. People with ADHD are also more likely to experience work challenges, such as unemployment, job layoffs, and reliance on social welfare benefits[32,33]. These issues lead to a decrease in the quality of life[25,34].

Current Treatment Approaches

The treatment of ADHD typically involves a multimodal approach, for example, according to the NICE (The National Institute for Health and Care Excellence) Guidelines, the first step is always the process of planning multimodal treatment, taking into account the psychological, behavioral, professional or educational needs of the child and their family[7]. This approach involves both pharmacological and non-pharmacological methods. Pharmacotherapeutic interventions use stimulants (methylphenidate and amphetamine preparations) and non-stimulants (selective alpha-2-adrenergic receptor agonists: guanfacine, clonidine and a selective norepinephrine reuptake inhibitor: atomoxetine). Non-pharmacological methods include psychological therapies and diet. Psychological therapies include behavioral therapy, cognitive training and neurofeedback, but only behavioral therapy showed statistically significant benefits and can be recommended as an evidence-based intervention[35]. Unfortunately, treatment methods have limitations including side effects, cost, and potential ineffectiveness in some individuals[5,35,36].

Due to the urgent need to develop strategies to improve the cognitive functioning, psychological well-being and symptomatology of people suffering from ADHD, the search for new treatment solutions is ongoing[37]. For example, over the years, there have been numerous publications suggesting nutrition as a factor in the pathophysiology and treatment of various mental disorders, including ADHD[38–43]. In the approach to the treatment of ADHD, hopes are placed on the role of diet, vitamins and minerals used in appropriate nutritional regimens[42,44–46].

Magnesium and ADHD

Magnesium is an essential cation taking part in numerous (over 300) enzymatic reactions, which makes it crucial for various physiological processes in the human body[47,48]. For example it participates in protein and nucleic acid synthesis, regulation of metabolic pathways, neuromuscular transmission and intercellular communication, and heart rhythm regulation[49–51]. Several aspects link magnesium and ADHD. Magnesium participates in the blockade of the N-methyl-d-aspartate (NMDA) receptor, responsible for stimulating glutamatergic signaling[52]. Increased glutamatergic neurotransmission can lead to excitotoxicity, oxidative stress, and neuronal cell death[53]. Abnormal glutamatergic neurotransmission has been associated with many neurological and psychiatric disorders[54]. Furthermore, oxidative stress is associated with the pathophysiology of ADHD and reduction in the antioxidant protection provided by magnesium may be one of the causes of ADHD[55]. Magnesium also takes part in the metabolism of essential fatty acids, which is needed in the process of neurodevelopment and proper functioning of the brain and is associated with hyperactive behavior[56]. Additionally, magnesium is associated with the production of serotonin and dopamine and norepinephrine release. Low magnesium level results in low levels of these neurotransmitters, potentially impacting ADHD symptoms[57–59].

Magnesium deficiency is associated with cognitive impairments, manifesting as symptoms like fatigue, concentration difficulties, nervousness, mood swings, and aggression[60]. This overlap in symptomatology with ADHD has prompted numerous studies investigating magnesium levels in individuals diagnosed with ADHD. While most studies report lower serum magnesium concentrations in ADHD patients compared to healthy controls, suggesting a potential deficiency link, some studies have shown conflicting results with similar or even higher serum magnesium levels in ADHD patients[61].

This review aims to provide a comprehensive and accessible summary of the latest literature (2019-2024) examining the relationship between magnesium and ADHD, focusing closely on the possible use of magnesium as a potential adjunct therapy for ADHD.

METHODOLOGY

Literature selection was performed by searching the PubMed database to identify relevant studies using combinations of such terms as: „magnesium", „magnesium status", „hypomagnesemia", „magnesium supplementation", „ADHD", „Attention Deficit/Hyperactivity Disorder", „observational study", „interventional study", „meta-analysis". Publications were included if they were observational studies or interventional studies or meta-analyses investigating the relationship between magnesium and ADHD published in English between 2019 and 2024. Publications not strictly related to the topic, duplicates and studies involving animals were excluded. Following the initial search, retrieved studies were screened based on titles and abstracts. Studies that met the inclusion criteria underwent a full-text review. Eight publications were considered for this work.

LITERATURE REVIEW

Observational studies:

Several published observational studies investigated magnesium levels in children with ADHD[62–65].

One of the studies assessed magnesium (Mg) levels in serum, hair and urine in children with attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), both diagnoses (ADHD+ASD) and healthy controls. The study included 148 boys aged 4–9 years, including 44 children with ADHD, 40 children with ASD, 32 patients with ADHD and ASD, and 32 healthy children. Diagnoses were based on ICD-10 for ADHD and confirmed using ICD-10 and CARS (The Childhood Autism Rating Scale) for ASD. Magnesium levels were measured by inductively coupled plasma mass spectrometry (ICP-MS). The obtained data showed no significant difference between the groups in the serum magnesium concentration.

However, hair magnesium content was lower in children with ADHD and ADHD+ASD compared to controls. Urine magnesium concentration was higher in the ADHD+ASD group compared to all others..The authors suggest these findings may indicate increased magnesium excretion in children with ADHD and that lower hair magnesium levels might be associated with more complex neurodevelopmental disorders like co-occurring ADHD and ASD. Notably, disease severity and dietary magnesium intake were not evaluated, limiting the study's conclusions.[62]

The next study compared serum levels of essential trace elements and minerals in children with ADHD compared to healthy controls. The number of examined children aged 4-9 years was 68 each in both groups, children with ADHD and healthy controls. Levels of trace elements and minerals such as: cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), iodine (I), manganese (Mn), molybdenum (Mo), selenium (Se), vanadium (V) and zinc (Zn) and minerals such as calcium (Ca), magnesium (Mg) in serum were assessed using inductively coupled plasma mass spectrometry (ICP-MS). The results of the study showed that children with ADHD had lower serum magnesium concentrations than the control group. This study had several limitations such as: small study population, no assessment of dietary magnesium intake, and only one substrate (serum) tested[63].

Another study examined the levels of various trace elements and minerals in the hair of boys with ADHD, ASD, and ADHD + ASD compared to healthy boys. The study included 207 boys: 52 with ADHD, 53 with ASD, 52 with ADHD+ASD and 52 healthy boys. Levels of trace elements and minerals such as: cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), iodine (I), potassium (K) lithium (Li) manganese (Mn), sodium (Na) phosphorus (P) selenium (Se) silicon (Si), vanadium (V) zinc (Zn) calcium (Ca) magnesium (Mg)) were measured in hair using inductively coupled plasma mass spectrometry (ICP-MS). Diagnoses followed ICD-10 and CARS for ASD and ICD-10 for ADHD. Notably, the study included only newly diagnosed children, prior to treatment initiation. The results of this study showed lower magnesium levels in ASD, ADHD and ADHD + ASD groups compared to healthy boys, with the most significant decrease observed in the ADHD+ASD group. This study had some limitations. Namely, hair may not accurately reflect internal mineral levels due to contamination and washing, analysis of paired hair samples with blood analysis could provide a more reliable picture. Additionally, there was no assessment of dietary trace element and mineral intake[64].

The last of studies explored the relationship between hair essential trace elements and mineral content and ADHD in preschool (4-6 years) and primary school children (6-10 years) stratified by age and gender. The study groups included 90 children aged 4–6 years (preschool) and 6–10 years (primary school), with ADHD (49 boys, 41 girls) and 90 healthy (49 boys, 41 girls) controls (matched by age and gender). All children were newly diagnosed with ADHD based on ICD-10 and without prior treatment. The levels of elements such as: boron (B), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), iodine (I), lithium (Li), manganese (Mn), selenium (Se) in hair were tested.), silicon (Si), vanadium (V) and zinc (Zn) and minerals such as calcium (Ca), potassium (K), magnesium (Mg), sodium (Na) and phosphorus (P) using induced-coupling mass spectrometry plasma (ICP-MS). The obtained data show that hair magnesium levels were significantly lower in children with ADHD compared to controls. Notably, the reduction was more pronounced in preschoolers with ADHD compared to older children. This study had some limitations. Namely, relatively small sample size, possible lack of reflection of the direct concentration of the element in the body through the level of the element in the hair. Moreover, lack of element and mineral intake assessment[65].

Interventional studies:

In 2020, two manuscripts were published that investigated the effects of combined vitamin D and magnesium supplementation on ADHD symptoms in children[66,67]. Randomized, double-blind, placebo-controlled clinical trials were conducted in which 66 children with ADHD participated. The effect of supplementation at the following doses was assessed for 8 weeks: magnesium 6 mg/kg/day and vitamin D 50,000 IU/week. The study group and the placebo group each consisted of 33 people. The Conners Parent Rating Scale was used to assess the impact on behavioral problems in children with ADHD, and the Strengths and Difficulties Questionnaire (SDQ) was used to assess mental health. These Scales and Questionnaires were administered at the beginning and end of the study. Both groups continued taking methylphenidate (adjusted for in analysis).

After the intervention, there was increased serum magnesium and vitamin D levels in the intervention group compared to the control group, without reported any adverse effects of vitamin D and magnesium supplementation at the end of the study. Conners Parent Rating Scale showed improvements in conduct problems, social problems, and anxiety/shyness compared to placebo. No significant change in psychosomatic problems. Strengths and

Difficulties Questionnaire (SDQ) showed reductions in emotional problems, peer problems, general difficulties, and internalizing scores compared to placebo. No significant change in conduct problems, prosociality, externalizing, or hyperactivity. Girls showed lower mean SDQ scores than boys. Both studies had some limitations. Namely, the effect of each supplement was not examined separately, only the combined supplementation of magnesium and vitamin D, dietary intake of magnesium and vitamin D not evaluatedand. Additionally, the sample size was relatively small and the follow-up period was short, so the long-term effects are unknown.

A 2021 open-pilot study explored the safety and efficacy of LTAMS (magnesium L-threonate) on ADHD symptoms and cognitive function in 15 adults with moderate ADHD (both medicated and unmedicated)[68]. LTAMS was administered for 12 weeks. Nearly half (47%) of participants showed significant improvement in ADHD symptom severity scales. The small sample size and lack of a placebo group limit the validity of results.

Meta-analyses:

Two recent meta-analyses have explored the association between magnesium levels and ADHD[69,70].

First meta-analysis aimed to determine if children with ADHD have lower magnesium levels compared to healthy controls. A comprehensive search across various databases (PubMed, ProQuest, ClinicalKey, Embase, ScienceDirect, Cochrane Library, Web of Science, ClinicalTrials.gov) identified 12 relevant studies published before October 27, 2018. The analysis revealed significantly lower serum and hair magnesium levels in children with ADHD compared to controls[69].

Second meta-analysis ssought to to summarize and quantify the literature on magnesium and ADHD. Studies published through August 2018 were identified via searches in Scopus and PubMed. Inclusion criteria focused on observational studies measuring serum magnesium levels in both ADHD and control groups. Only seven studies met these criteria. This analysis again demonstrated significantly lower serum magnesium levels in individuals with ADHD compared to healthy controls[70].

These meta-analyses have some limitations. First of all, no cause-and-effect relationship has been established between magnesium levels and ADHD, and meta-analyses were characterized by significant heterogeneity, suggesting variability among included studies. The number of studies included in each analysis was relatively small. Moreover, reduced magnesium levels may be caused by various factors not accounted for in the analyses due to limited data. Additionally, variations in techniques used to measure magnesium levels across studies need to be considered.

CONCLUSIONS

Scientific literature shows growing interest in the relationship between magnesium and ADHD, with a steady increase in research. Many available studies suggest a link between magnesium deficiency and ADHD symptoms, potentially indicating a role for magnesium in ADHD pathophysiology. However, the exact nature of this association remains unclear. A direct cause-and-effect relationship has not been established, highlighting the need for further research to elucidate the mechanisms underlying this link and to verify the potential benefits of magnesium supplementation in alleviating ADHD symptoms. Additionally, other factors such as diet, genetics, or socioeconomic background may also contribute to ADHD pathophysiology and warrant investigation. To definitively assess the effectiveness and safety of magnesium supplementation as a complementary therapy for ADHD, high-quality, large-scale, long-term clinical trials using consistent methodologies are crucial. These studies should determine the optimal doses, forms, and duration of magnesium supplementation to ensure safe and effective clinical use.

Author's contribution

Conceptualization: Karolina Smykiewicz and Aneta Michalczewska; Methodology: Justyna Dobrzańska; Software: Agnieszka Nowak; Check: Zuzanna Chmielowiec and Agnieszka Fugas; Formal analysis: Natalia Wierzejska and Alicja Partyka; Investigation: Magdalena Pach and Mariola Dziedzic; Resources: Alicja Partyka; Data curation: Mariola Dziedzic Writing - rough preparation: Karolina Smykiewicz and Justyna Dobrzańska; Writing - review and editing, Aneta Michalczewska and Magdalena Pach; Visualization: Zuzanna Chmielowiec; Supervision: Agnieszka Nowak; Project administration: Agnieszka Fugas; and Natalia Wierzejska; Receiving funding - no specific funding.

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