

Magnesium Serum Concentrations in Patients with Dementia Vs. Controls; A Systematic Review and Meta-Analysis

Keywords: Dementia; Magnesium; Serum magnesium; Systematic review; Meta-analysis

Abstract

Background: The role of magnesium in the pathogenesis of dementia and other degenerative disorders has focused attention in recent years. There have been several studies reporting favorable effects of magnesium in the treatment of various degenerative illnesses. In contrast, other research found that both low and high serum magnesium levels were associated with an increased risk of Alzheimer's disease and mixed dementia. These contrasting results render the role of magnesium levels in dementia unclear. Our objective was to investigate the possible association between dementia and hypomagnesaemia.

Methods: We conducted a systematic review and meta-analysis of all articles, in any language, reporting on serum magnesium concentrations either in plasma or serum of patients with dementia, compared to patients without dementia. Studies reporting on proportion of hypomagnesaemia patients and not mean levels were excluded.

Results: Seven studies were accepted for the meta-analysis, reporting on 2932 dementia cases and 42920 controls. All types of dementia were reported. There was a significant heterogeneity in the results, and the difference in Mg²⁺ concentrations between patients with dementia and controls was not significant (mean difference -10.68 micromole/L (95% confidence interval -30.62 and +9.27). There were no significant differences in the measured levels of the different types of dementia.

Conclusions: Our study, based on large numbers of dementia patients and controls, suggests that low serum magnesium concentrations are not associated with increased risk of dementia. This may be explained by poor correlation between serum and tissue distribution of magnesium and by the fact that less than one percent of total body magnesium circulates in the blood.

Introduction

The role of magnesium in the pathogenesis of dementia and other degenerative disorders has focused increased attention in recent years [1-2]. There have been two main hypotheses for the role of magnesium in dementia:

1) A direct effect of neuronal magnesium on regulation of the ionotropic glutamatergic receptor N-methyl-D-aspartate (NMDA). It has been demonstrated that ionized magnesium leads to closure of cation channels which have been opened by glutamate on NMDA receptors [3].

2) Magnesium deficiency leads to oxidative stress which stimulates secretion of inflammatory mediators such as interleukins, tumor necrosis factors, and nitric oxide. These mediators are thought to stimulate atherosclerosis and thereby increase the risk of dementia

[3]. Low magnesium levels were found to be decreased in various tissues of patients with Alzheimer's disease in clinical, experimental, and autopsy studies [4]. A reduction in the frequency of intracellular magnesium deposits in neurons of Alzheimer's patients was reported. Decrease in magnesium and glutamic acid have been shown in the hippocampal tissue of Alzheimer's disease patients [5]. There is evidence that glutamate release and intake are chronically disturbed in Alzheimer's disease, and glutamate levels are possibly increased in the synaptic cleft, with resultant calcium influx to postsynaptic neurons and activation of the calcium - related enzyme system. This leads to production of free radicals, protein destruction, lipid peroxidation, and neuron death with DNA destruction [4].

Increasing volume of research has explored the connection between magnesium and the role of NMDA receptors in degenerative brain disorders. NMDA receptors have a critical role the central nervous system, including neuronal development, plasticity and neurodegeneration [1, 3]. These receptors lead to channels which are permeable to calcium, sodium and potassium ions and voltage-gated channels blocked by magnesium ions. Transient glutamate release from the presynaptic region occurs during normal learning and memory process. This release causes depolarization on the postsynaptic membrane, after which ionized magnesium (Mg²⁺) leaves voltage gated channels on NMDARs, and Ca²⁺ influx inside the neuron occurs. Increase in Ca²⁺ levels inside the neuron initiates a signal transmission process and this facilitates memory and learning. At the end of stimulation, Mg²⁺ stops Ca²⁺ influx inside the neuron by closing channels on the NMDA receptors [1, 3].

There have been several studies suggesting favorable effects of magnesium in the treatment of various degenerative illnesses. Improvement in memory was reported with nutritional magnesium support in patients with dementia [6-7]. Similarly, higher self-reported dietary intake of magnesium was found to be associated with a decreased risk of dementia [7]. Moreover, the risk for the development of vascular dementia was decreased with hazard ratio of 0.26 (95% CI 0.11-0.61) for the highest quartiles of magnesium intake [7]. In contrast, other research found that both low and high serum magnesium levels were associated with an increased risk



Journal of Parkinson's Disease & Alzheimer's Disease

Ben-Zaken S¹, Kaplan Y² and Koren G^{1,2*}

¹Department of Pediatrics, Adelson School of Medicine, Ariel University, Israel

²Motherisk International

*Address for Correspondence

Koren G, MD FRCP FACMT, Ariel University, Ariel Israel, 40700; Tel 972587194777; Email: gidiup_2000@yahoo.com

Submission: 13 July, 2021

Accepted: 25 August, 2021

Published: 30 August 2021

Copyright: © 2021 Ben-Zaken S, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

of Alzheimer’s disease and mixed dementia [8]. These contrasting results render the role of magnesium levels in dementia unclear.

For that end, our objective was to conduct a systematic review and meta-analysis in order to verify whether dementia and Alzheimer disease are associated with lower serum magnesium concentrations.

Materials and Methods

We conducted a search for all articles, in any language, reporting on serum magnesium concentrations in patients with dementia, compared to control groups of patients without dementia. We searched PubMed, Medline, Embase, Google and Google Scholar from inception to August 1, 2020. We included original papers and excluded case reports, letters to the editor, reviews and animal studies, or any paper where there was no comparison of magnesium levels to control group of subjects without dementia.

We reviewed the papers for demographics and details on diagnosis and measured magnesium levels. We included papers that reported means of magnesium levels. Papers that reported only proportions of patients with hypomagnesemia but without specific mean levels were excluded.

Data were extracted from eligible studies which reported mean and SD of magnesium levels in patients with dementia and their respective control groups. Data were combined by using a random effects model with RevMan 3.3 (Review Manager 5.3; Cochrane Collaboration, Oxford, UK) and the effect size was represented by the mean difference (MD) since the unit of the outcome was similar in all included trials [9]. Heterogeneity was assessed utilizing the Q and I-square statistic. An I square value between 25%-50% signifies low heterogeneity, between 50%-75% moderate and >75% signifies high heterogeneity. A funnel plot was not used to evaluate publication bias since the number of included studies was below 10, which yields a low power detecting asymmetry with good accuracy [10]

Results

We identified 214 potentially eligible titles. During title and abstract review 12 full text studies were reviewed, and 7 studies described in 6 peer review papers were accepted for the meta-analysis [11-15] as Vural et al described 2 separate populations in a single paper [14] (Table 1). All types of dementia were included (Alzheimer’s, Vascular, Mixed). The determinations of Mg2+ levels were made mostly after a period of hospitalization. Dietary supplement with magnesium was not detailed in most studies.

The studies (n=7), conducted between 1990 and 2020, compared serum or plasma magnesium levels between patients with dementia and controls. They included 2932 dementia patients and 42900 controls. Ratio between women and men was 1.278. There were no differences in mean magnesium levels related to patient age. There was a significant heterogeneity in the results, and the difference in Mg2+ concentrations between patients with dementia and controls was not significant (mean difference -10.68 micromole/L (95% confidence interval -30.62 +9.27). (Table 1). Most studies did not report on medications received by the patient, that may affect magnesium levels.

In 5 of the studies we could compare magnesium levels among Alzheimer patients versus controls. The results were heterogenous.

In 3 studies magnesium levels were slightly lower among Alzheimer patients in 1.2% (Vural [14]), 2 % (Barbagallo [4]) and 5.9% (Cillier [12]). In one study (Borella [11]) the results were equal (0%), while in one study (Gustaw [15]) the magnesium results were substantially higher among Alzheimer patients (33%).

Discussion

There is an ongoing controversy and uncertainty whether hypomagnesemia causes or is a contributing factor in dementia [1, 4-6]. In addition to measurement of serum magnesium, the literature has identified several studies comparing magnesium levels in mononuclear cells [35.36+/-3.56 micromoles/g in dementia and 33.97+/- 5.16 among young controls, and 37.07+/- 4.5 among older controls] [11] and in polymorphonuclear cells[25.54+/- 3.71micromole/g in dementia, 26.03+/- 5.37 in young and 22.35+/- 3.47 in older controls [11].

Andrasi and colleagues compared magnesium levels in 3 brain samples of patients with dementia (540-625 mcg/g dry weight) vs. 3 controls (628-680) [16], and Hozumi compared cerebrospinal fluid (2.064+/- 0.18 mg/dL in dementia and 2.065 +/- 0.18 among controls) [17].

In a previous systematic review Verones and colleagues identified an additional paper comparing magnesium levels in CSF, as well as hair magnesium [18]. In their review they included four articles comparing serum magnesium in 190 Alzheimer patients and 189 controls, not showing significant differences. It was possible that this lack of difference might have been the result of small sample size and a resultant limited statistical power. Our present analysis has

Table 1: Forest plot of the association of dementia with lower concentrations of serum magnesium

Study or subgroup	Dementia			Control			
	Mean[Micromol/L]	SD[Micromol/L]	Total	Mean[Micromol/L]	SD[Micromol/L]	Total	weight
Borrela et al.1990	760	50	19	760	60	24	16.1%
Cilliler et al. 2007	926	127	37	915	134	34	7.8%
Vuval et al.2010(male subjects)	785	80	23	871	131	24	7.6%
Gu straw- Rothengerg et al. 2010	998	238	30	780	102	29	4.0%
Vuval et al.2010(female subjects)	780	86	27	879	131	26	8.0%
Barbagallo et al.2011	955	15	35	975	15	65	27.9%
Ben Zaken et al. 2020	848.3	73	2761	848.7	73	42698	28.5%
Total(95% CI)			2932			42900	100.0%

Heterogeneity: Tau² = 361.31; Chi² = 70 df = 6(P < 0.00001); I² = 92%
 Test for overall effect: Z =105 (P = 0.29)

identified 7 reports with tenfold more dementia subjects and 220-fold more controls. Our results, failing to show significant changes in serum magnesium with very large numbers of subjects and controls corroborate the much smaller sample size in Veronese study.

Of potential importance, Veronese' study also compared small numbers of studies comparing cerebrospinal fluid levels (n=2) and hair concentrations (n=2) showing significantly lower levels in Alzheimer patients vs. controls [18].

Using serum magnesium as a biological marker of magnesium status has inherent shortcomings, as it does not reflect intracellular or total body magnesium status [19-20]. Indeed, Veronese et al did find lower levels of magnesium in CSF and hair of dementia patients [18], and brain levels do not appear to be lower [16].

In contrast to these observational studies, there is evidence that higher self-reported dietary intake of magnesium had been associated with a decreased risk of dementia [7].

Several limitations of this study must be acknowledged. For obvious reasons serum magnesium is much more available than tissue magnesium; however the lack of strong correlation between serum magnesium and tissue magnesium makes it difficult to interpret serum magnesium. The heterogeneity of the reported serum magnesium among the different studies may reflect inconsistencies in time of measurement of magnesium (e.g. upon admission to hospital vs. in the community, in dietary supplementation and inclusion/exclusion of drugs affecting magnesium levels).

Our study, based on large numbers of dementia patients and controls, suggests that low serum magnesium concentrations are not associated with increased likelihood of dementia. Hence, serum magnesium should be used with caution to predict the status and activity of dementia in patients. More studies are needed in order to identify biological markers of magnesium disposition in dementia, particularly on the direct comparison of different types of dementia.

References

1. Kirkland AE, Sarlo GL, Holton KF (2018) The Role of magnesium in neurological disorders. *Nutrients* 10: 730.
2. Uwitonze AM, Razzaque MS (2018) Role of magnesium in vitamin D activation and function. *J Am Osteopath Assoc* 118: 181-189.
3. Vyklicky V, Korinek M, Smejkalova T (2014) Structure, function, and pharmacology of NMDA receptor channels. *Physiol Res* 63: 191-203.
4. Barbaggio M, Belvedere M, Di Bella G, Dominguez LJ (2011) Altered ionized magnesium levels in mild-to moderate Alzheimer's disease. *Magnes Res* 24: 115-121.
5. Durlach J (1990) Magnesium depletion and pathogenesis of Alzheimer's disease. *Magnes Res* 3: 217-218.
6. Ozturk S, Cillier AE (2006) Magnesium supplementation in the treatment of dementia patients. *Med Hypotheses* 67: 1223-1225.
7. Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, et al. (2012) Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the Hisayama Study. *J Am Geriatr Soc* 60: 1515-1520
8. Kieboom BCT, Licher S, Wolters FJ, Ikram MK, Hoom EJ, et al. (2017) Serum magnesium is associated with the risk of dementia. *Neurology* 89: 1716- 1722
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG et al. (2003) Measuring inconsistency in meta-analysis. *327:557-560*
10. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I, et al. (2006) The case of the misleading funnel plot. *BMJ* 333: 597-600.
11. Borella P, Giardino A, Neri M, Andermarker E, et al. (1990) Magnesium and potassium status in elderly subjects with and without dementia of Alzheimer type. *Mages Res* 3: 283-289.
12. Çilliler AE, Öztürk S (2007) Serum Magnesium Level and Clinical Deterioration in Alzheimer's Disease. *Gerontology* 53: 419-422.
13. Ben Zaken S, Radomysalsky Z, Koren G. Association Between Serum Magnesium Levels and Alzheimer's Disease or Mixed Dementia Patients: A Population-Based Retrospective Controlled Study *J Alzheimer's Dis Rep* 4: 399-404.
14. Vural H, Demirin H, Kara Y, Eren I, Delibas N, et al. Alterations of plasma magnesium, copper, zinc, iron and selenium concentrations and some related erythrocyte antioxidant enzyme activities in patients with E, disease. *J Trace Elem Med Biol* 24: 169-173.
15. Gustaw-Rothenberg K, Kowalczyk K, Stryjecka-Zimmer M (2010) Lipids' peroxidation markers in Alzheimer's disease and vascular dementia *Geriatr Gerontol Int* 10: 161-166.
16. Andrasi E, Palf N, Molnar Z, Kösel S, et al. Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. *J Alzheimer Dis* 7: 273-284.
17. Hozumi I, Kohmura A, Kimura A, Hasegawa T, Honda A et al. (2010) High levels of copper, zinc, iron and magnesium in the cerebrospinal fluid of patients with Fahr's disease. *Case Rep Neurol* 7: 46-51.
18. Veronese N, Zurlo A, Solmi M, Luchini C, Trevisan C, et al. (2016) Magnesium status in Alzheimer disease: A systematic review. *Am J Alzheimer dis* 31: 208-213.
19. Noronha JL, Matuchak GM (2002) Magnesium in critical illness: metabolism, assessment and treatment. *Int Care Med* 28: 667-669
20. Razzaque MS, Uwitonze AM (2018) Role of magnesium in vitamin A activation and function. *J Am Osteopath Assoc* 118: 181-189.