

Research Report

Association Between Serum Magnesium Levels and Alzheimer's Disease or Mixed Dementia Patients: A Population-Based Retrospective Controlled Study

Sara Ben Zaken^a, Zorian Radomysky^b and Gideon Koren^{a,*}

^a*Adelson School of Medicine, Ariel University, Ariel, Israel*

^b*Maccabi Health Services, Ariel, Israel*

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Abstract.

Background: High magnesium intake has been associated with a decreased risk of dementia. In contrast, other research has found that both low and high serum magnesium levels were associated with an increased risk of Alzheimer's disease and mixed dementia. Hence, presently the role of magnesium levels in dementia is unclear.

Objective: To investigate a possible association between serum magnesium concentrations and dementia in a large population-based sample.

Methods: Maccabi Healthcare Service in Israel provides healthcare to over 2 million citizens. Maccabi maintains a registry with approximately 26,000 diagnosed dementia patients. We focused on patients of both sexes with Alzheimer's disease or mixed dementia aged 65 or older, excluding patients with clinical diagnoses that could affect serum magnesium level, or with other causes of cognitive decline. Our control group consisted of patients of the same age and sex without dementia.

Results: No significant differences were found in mean, mode, and median magnesium levels between the dementia and control groups. However, there were marginally but significantly more cases with low magnesium levels among dementia patients than among controls: A total of 9.4% of tests done in patients with dementia and 7.81% done in non-dementia subjects were hypomagnesemic ($p < 0.00001$).

Conclusion: Despite similar means and medians of serum magnesium in dementia and controls, the proportion of lower than normal magnesium test results was slightly higher among dementia patients. It is possible that patients with dementia have more episodes of hypomagnesemia than controls, despite similar overall mean levels of magnesium.

Keywords: Alzheimer's disease, magnesium, mixed dementia, serum magnesium

INTRODUCTION

Magnesium is the fourth most abundant mineral in the human body after calcium, potassium, and sodium [1]. It is essential for the stability of cell function,

RNA and DNA synthesis, and cell repair, as well as for maintaining the antioxidant status of the cell. In addition, it is an important cofactor for many biological processes and for the activation of a wide range of transporters and enzymes [1, 2]. Magnesium plays a critical role in nerve transmission, cardiac excitability, maintaining normal heart rhythm, neuromuscular conduction, muscular contraction,

*Correspondence to: Gideon Koren, MD, FRCPC, FACMT, Ariel University, Ariel 40700, Israel. Tel.: +972 587194777; E-mail: gidiup_2000@yahoo.com.

blood pressure, and glucose and insulin metabolism [3].

Alzheimer's disease is the most common form of dementia. While its etiology has not been identified, it is associated with environmental factors, nutrition, and vitamins among other elements [4].

Differentiation of Alzheimer's disease from other common forms of dementia is important in order to implement an appropriate treatment plan and provide prognostic information for the patients [5]. Vascular dementia, caused by cerebrovascular disease, is the second most common cause of dementia. Cerebrovascular disease is a risk factor for Alzheimer's disease, but can also coexist with Alzheimer's disease, creating a form of "mixed" dementia.

The role of magnesium in dementia and other degenerative disorders have been the focus of increased attention in recent years [6]. There are two main hypotheses for the role of magnesium in dementia:

- 1) The direct effect of neuronal magnesium on regulation of the N-methyl-D-aspartate (NMDA) receptors, which is an ionotropic glutamatergic receptor. Magnesium is a soft-block of the receptor that is in place until depolarization, which removes the block, in addition to closing the calcium channel after neurotransmission has occurred. It has been demonstrated that ionized magnesium leads to closure of cation channels which have been opened by glutamate on NMDA receptors [7].
- 2) The second hypothesis is related to oxidative stress. Magnesium deficiency has been found to stimulate 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 [7].

Magnesium levels were found decreased in various tissues of patients with Alzheimer's disease in clinical, experimental, and autopsy studies (hypomagnesia) [8]. A reduction in the frequency of intracellular magnesium deposits in the neurons of Alzheimer's disease patients was observed when compared to normal controls. Decrease in Mg, K, and glutamic acid have been shown in the hippocampal tissue of Alzheimer's disease patients [9].

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 resulting Ca^{2+} influx to postsynaptic

neurons, which results in activation of the calcium related enzyme system and of free radicals, protein destruction, lipid peroxidation, and neuron death with DNA destruction [8].

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 in physiological and pathological processes of the central nervous system, including neuronal development, plasticity and neurodegeneration [5, 7]. 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 Mg^{2+} leaves voltage-gated channels on NMDARs, and Ca^{2+} influx inside the neuron occurs. Increase in Ca^{2+} levels inside the neuron initiates a signal transmission process and this facilitates memory and learning. At the end of stimulation, Mg^{2+} stops Ca^{2+} influx inside the neuron by closing channels on the NMDA receptors [5, 7].

There are several studies reporting favorable effects of magnesium in the treatment of various degenerative illnesses. Improvement in memory and other symptoms was reported with nutritional magnesium support in patients with dementia [10, 11]. Higher self-reported dietary intake of magnesium was found to be associated with a decreased risk of dementia [11]. In this study, community-dwelling Japanese individuals without dementia aged 60 and older were assessed. During a 17-year follow-up, 303 participants experienced all-cause dementia. In multivariable-adjusted analysis, the hazards ratio (HR) for the development of all-cause dementia was 0.63 for the highest quartiles of magnesium intake, compared with the corresponding lowest quartiles. Similarly, the HR for the development of vascular were 0.26 (95% CI = 0.11–0.61) for the highest quartiles of magnesium intake [11].

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 [12]. These contrasting results render the role of magnesium levels in dementia unclear. Large-population based research is essential to try to better verify whether magnesium may contribute to the pathogenesis of dementia in general and Alzheimer's disease in particular.

The objective of the present study was to investigate a possible association between serum magnesium concentrations and dementia in a large population-based sample.

METHODS

This was a retrospective population-based controlled study of magnesium serum concentrations, comparing dementia patients with non-dementia controls. The study was approved by Assuta Hospital Research Ethics Committee in Tel Aviv.

Settings

Maccabi Healthcare Service is Israel's second largest health insurance organization, providing healthcare to over 2 million citizens [13, 14]. Maccabi has a central computerized database which contains demographic and medical data, including diagnoses, drug purchases (all prescriptions and part of OTC drugs), laboratory data, hospitalizations, and physician visits.

Maccabi maintains a registry of dementia patients, diagnosed by a geriatrician, a psychiatrist, or a neurologist. Our study focused on patients of both sexes with Alzheimer's disease or mixed dementia aged 65 or older. We identified all cases of dementia (ICD-9 code 294.20). Alzheimer's disease (ICD-9 code 331.0) is the most common form of dementia. Vascular dementia (ICD-9 code 290.42), caused by cerebrovascular disease, is the second most common cause of dementia.

The dementia registry contains medical information of 25,800 patients. We excluded 23,039 patients with either clinical diagnoses that could affect serum magnesium level [1]: use of diuretics, laxatives, Crohn's disease, or with other causes of cognitive decline, such as alcohol abuse history, hypo and hyperthyroidism, hepatic and heart failure, patients on dialysis or with significant decline in renal function, patients with Parkinson's disease, brain injury, hypoglycemia and other rare types of dementia.

Our control group consisted of patients of the same age (± 1 year), same sex, with the same inclusion criteria but without dementia (42,698 patients). The groups included similar proportions of sexes (Table 2).

Serum magnesium was measured in Maccabi Healthcare Service Mega Lab by a photometric color on Olympus AU5800 Beckman Coulter analyzer (Beckman Coulter, Inc., Brea, CA, USA).

Table 1
Reference intervals of serum magnesium test

Sex	Normal range
Males	0.73–1.06 mmol/L (1.8–2.6 mg/dL)
Females	0.77–1.03 mmol/L (1.9–2.5 mg/dL)

Briefly, the magnesium reagent utilizes a direct method in which magnesium ions form a colored complex with xylydyl blue in a strongly basic solution. The color produced is measured bichromatically at 520/800 nm and is proportional to the magnesium concentration in the sample. Calcium interference is eliminated by glycoetherdiamine-N,N,N',N'-tetraacetic acid (GEDTA) [15–17].

Magnesium normal range of serum concentrations may vary with age, sex, sample type, nutrition, and geographical location. The laboratory verified the transferability of the expected values to its own population, and if necessary determines its own reference interval according to good laboratory practice. Magnesium reference intervals at Maccabi's Mega Lab have been stable since 2004, as shown in Table 1 [17].

Magnesium levels below 1.8 mg/dL in men and 1.9 mg/dL in women were defined as hypomagnesemia, whereas levels above 2.6 mg/dL in men or 2.5 mg/dL in women were defined as hypermagnesemia (Table 1).

Analysis

From the electronic charts we extracted all results of serum magnesium levels of the study and control groups between January 2001 and December 2019. In patients with more than one level of magnesium, we calculated the mean, maximum, and minimum levels over this time period. The two groups were compared using Student's *t*-test for normally distributed continuous variables, Mann Whitney U tests for non-normally distributed values (medians), and by Chi square for dichotomous variables.

RESULTS

General characteristics of participants in both test and control groups are described in Table 2.

No significant differences were found in mean, mode, and median magnesium levels between the dementia and control groups. However, there were a slight by statistically significant more cases with low magnesium levels among dementia patients than among controls.

Table 2
Magnesium levels in the study and control groups

Parameter	Dementia*	Controls	Significance
Number of participants	2,761	42,698	
M/F	988/1773 (35.8/64.2%)	16,160/26,538 (37.8/62.2%)	N.S.
Mean Age (before matching)	78.88	72.05	$p < 0.01$
Mean Mg (mg/dL)	2.064 ± 0.18	2.065 ± 0.18	N.S.
Mode Mg (mg/dL)	2	2	N.S.
Median Mg (mg/dL)	2.1	2.1	N.S.
Minimal Mg result (mg/dL)	0.9	0.3	N.S.
Maximal Mg result (mg/dL)	2.9	3.6	N.S.

*Alzheimer 43%, vascular dementia 47%, mixed dementia 10%. No differences have been detected between the mean, mode and median serum Mg concentrations in dementia cases versus controls.

Table 3
Proportions of serum magnesium tests below and above the normal ranges among males, females, and all patients

Number of of Mg results	Males		Females	
	control	test	control	test
Normal range	37,874	2,483	64,496	4,527
Hypomagnesemia	1478	107	7,869	629
	3.75%***	4.12%***	10.84%*	12.14%*
Hypermagnesemia	46	1	203	21
	0.11%	0.038%	0.027%**	0.4%**
Total	39,398	2,591	72,568	5,177

Female hypomagnesemia: $*p = 0.0035$; Male hypomagnesemia: $***p = 0.089$ (N.S.); Female hypermagnesemia: $**p = 0.04$; Male hypermagnesemia: $p = 0.3$ (N.S.); Total hypomagnesemia (males and females): $***p < 0.00001$; There was a marginal, but significantly higher proportion of cases of hypomagnesemia among patients with dementia (9.4%) as compared to controls (7.81%). The total numbers differ from Table 2 because here all samples were counted whereas in Table 2 the mean levels of more than one sample are presented.

In general women tended to have on average 85% more magnesium tests done than men, probably due to higher prevalence and recognition of osteoporosis. Approximately 12% of tests done in women with dementia and 10% done by healthy women were lower than normal range, hence hypomagnesemic ($p = 0.0035$). In men the difference was not significant, probably due to the substantially smaller sample ($p = 0.08$). When combining men and women, the difference was highly significant (9.4% versus 7.81%) when comparing the dementia group to the control group ($p < 0.00001$) (Table 3). Hypermagnesemia was negligible in both genders and both dementia and control groups. In a trend analysis, time did not impact magnesium serum levels for both groups separately between 2001 and 2019.

DISCUSSION

In the present study we could not detect significant differences in mean, mode, and median magnesium levels between the dementia and control groups. However, there were marginally but

significantly more cases with low magnesium levels among dementia patients than among controls with 9.4% of tests done in patients with dementia and 7.81% done in non-dementia subjects were hypomagnesemic ($p < 0.00001$). Hypermagnesemia was negligible in both genders and both dementia and control groups.

There are studies establishing hypomagnesemia within Alzheimer's disease and dementia using ionized Mg, cerebrospinal fluid, hair, plasma, and red blood cell Mg samples [18, 19].

Higher self-reported dietary intake of magnesium was found to be associated with a decreased risk of dementia [11]. Kieboom et al. found that both low and high serum magnesium levels were associated with an increased risk of Alzheimer's disease and mixed dementia [2].

The question leading to this research was whether dementia is associated with lower serum concentrations of Mg, as has been suggested in some studies. We have utilized a large population-based database to address this question. A registry of dementia patients, with over 25,000 cases, has allowed us to match individuals without dementia based on variables that may

affect magnesium levels, such as use of diuretics, laxative, and diseases such as Crohn's. It was also hoped that it will have statistical power to discern small effects of magnesium on dementia.

Overall, our results indicate that dementia patients did not exhibit lower means, medians, or modes of serum magnesium levels, and thus not being able to support the hypothesis that hypomagnesemia has a major role in the pathogenesis of dementia.

These results are consistent with the findings of our recent study in which we analyzed in a treat-control context how the switch to desalinated drinking water affected serum magnesium concentrations and the prevalence of dementia [20].

We selected two cities which differed in terms of their access to underground aquifers but were otherwise similar. One city has no underground water and uses over 90% desalinated water whereas the other relies almost entirely on its own aquifers. Using medical records for all subjects insured by the Maccabi Health Services, we examined mean serum concentrations of Mg in the period prior to desalination (2001-2006) and post desalination (2007-2018).

Serum magnesium levels were significantly lower following the switch to desalinated water yet the prevalence of dementia was similar in the two cities.

While this ecological study could not rule out some effect of hypomagnesemia on dementia morbidity, it suggested, similar to the present study, that the effect if exists, is relatively small.

In the present study, despite similar means and medians of serum magnesium in dementia and controls (Table 2), the proportion of lower than normal magnesium test results was marginally but significantly higher among dementia patients ($p < 0.00001$) (Table 3). It is possible that patients with dementia exhibit more episodes of hypomagnesemia than controls, despite similar overall mean levels of magnesium. It could be hypothesized that there was an uneven replicate sampling in that follow-up of low levels may be more frequent; however, then this should occur in both dementia and control groups. Also, the frequency of testing for magnesium did not change after diagnosis of dementia. Similarly, the annual attrition rate of patients in Maccabi Health Services is less than 1% and it was not different between the dementia and control patients. Moreover, all tests were done in one central reference laboratory. Last, there were no geographical differences in distribution between the dementia and control groups.

A strength of our study is in very large numbers and a unique dementia registry, where diagnosis is

confirmed by a geriatrician, neurologist or psychiatrist. The large cohort has also allowed us to exclude subjects that have known confounders of either low magnesium levels, or effects on cognition.

Potential weaknesses of the present study need to be acknowledged. Availability of magnesium serum concentrations did not include all patients, and the number of samples was not standardized. Clearly women had significantly more measurements, most probably due to much larger numbers of investigations into osteoporosis, which is much more prevalent among females. Another potential weakness is in the retrospective nature of the study; therefore collection of magnesium serum samples was not standardized and could have been impacted by unknown confounders. Using serum Mg has inherent limitations and although total serum magnesium concentration is the most commonly used test, this laboratory marker has limited clinical benefit as it does not accurately reflect intracellular or total body magnesium status [4, 21].

We also do not have records whether the dementia group were taking magnesium supplements or had a diet high in magnesium, which could normalize their serum values. Further comparison of the dementia group to the controls in rates of other conditions (e.g., diabetes) or use of medications (e.g., proton pump inhibitors, diuretics) is not likely to shed light on the findings of this study.

The question whether magnesium supplements can prevent or reduce the progress or severity of dementia requires more studies employing different methodologies.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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