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A study of serum magnesium, calcium and phosphorus level, and cognition in the elderly population of South India

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Abstract *Introduction:* Different studies have shown the role of micro and macronutrients on cognitive function. Macronutrients have been involved in many metabolic activities of the body including oxidation and reduction reactions in the central nervous system. This involvement of macronutrients in the activities of central nervous system indicates its role in cognition. The present study is designed to know the role of macronutrients and its relation with cognition by using biological samples.
Materials and methods: A total of 337 subjects with a mean age of 49 participated in the cross sectional study from different parts of Kerala state in India. Individuals participating in this study were administered a series of neuropsychological test batteries with major emphasis on 7-min screen test. All test procedures were administered by standard protocol after a written consent was obtained from the participating subjects. Analysis of macronutrients level of magnesium, calcium and phosphorus was done by using serum samples and the data obtained were then statistically analyzed using SPSS software version 17.
Results: The macronutrients magnesium, calcium and phosphorus were found to be significantly related to the cognitive score. Increasing magnesium and calcium level was associated with higher cognitive score ($P < 0.0031$ and 0.001 respectively), while lower phosphorus level was significantly associated with lower composite score ($P < 0.001$).
Conclusion: The results of our study give us an expression that macronutrients such as calcium, magnesium and phosphorus may be associated with cognitive function in elderly population of our state. But further studies on a larger population are required to come out with a definite conclusion.

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1. Background

Nutrients involved in the etiology and pathogenesis of several age-related central nervous system (CNS) abnormalities.[1–3] Magnesium (Mg^{2+}), the fourth most abundant ion in the body and a cofactor for more than 300 enzymes, is essential to all organisms.[4] It is one of the most important ions in the central nervous system and dietary deficiency of Mg^{2+} increases the neurotoxicity.[5] Mg^{2+} concentration is higher in the cerebrospinal fluid than in plasma, which is maintained by an active transport process. Magnesium serves several physiologic and homeostatic functions, including the regulation of neuromuscular and vascular tone[6] and the noncompetitive blockade of the NMDA-receptor channel, thereby acting as a calcium (Ca) antagonist.[7–10] Magnesium is also essential for membrane stability and fluidity, RNA aggregation and DNA and protein synthesis. Because of its involvement in a number of bioenergetic and biochemical activities, magnesium appears to play an important role in normal neuronal activity.[11] Mg^{2+} is a positive regulator of synaptic plasticity; increasing Mg^{2+} concentration in the extracellular fluid within the physiological range leads to permanent enhancement of synaptic plasticity in networks of cultured hippocampal neurons in vitro.[12] It has been suggested that Alzheimer's disease (AD) involves a defective transport process characterized by both an abnormally low Mg incorporation and abnormally high aluminum (Al) incorporation in brain neurons.[13] The origin of this disturbance rests on an alteration of serum albumin, forming a species which has greater affinity for Al than for Mg, in contrast to the normal protein which binds with Mg better than Al. The altered albumin crosses the blood–brain barrier more efficiently than the normal protein and competes with it in binding to brain neurons. Binding of altered albumin to the target neurons would both impede Mg uptake and facilitate Al uptake. Low level of Mg overexcites the brain's neurons and results in less coherence. It was hypothesized that the Mg depletion by increasing Ca/Mg ratio in the CNS tissues further accelerates the uptake of Al into the CNS, which promotes the neurodegenerative processes.[5,14] Another important element in the serum is phosphorus (P), which is a vital constituent of nucleic acids, organic phosphates, and adenosine triphosphate (ATP). As magnesium, calcium and phosphorous are important macronutrients for the CNS functioning, the present study is designed to evaluate their levels in maintaining cognition in elderly population of South India.

2. Materials and methods

2.1. Participants

Participants were a part of the cross-sectional study of Calicut University Project to Investigate Memory and Ageing (CUPTIMA), as adapted and standardized for Malayalam speaking population.[15] We administered a series of Neuropsychological test batteries (7-min Screen Test, CERAD Memory function test, Trail Making Test-TMT, Global versus Local attention task test, Handedness test, Mini Mental State Examination-MMSE and Geriatric Depression Scale-GDS) to 337 healthy individuals belonging to various places of Kerala state in India, especially Thrissur, Palakkad, Malappuram and Kozhikode districts, for about a 7 year period. All of them except three were right handed and none of them were inarticulate. Only participants who were having no history of stroke, head trauma, neurological disease, psychological illness, or any other known present illness and those who know Malayalam or English or both were chosen as participants. Individual participants were subjected to different test batteries.

Participants ranged from ages of 20 to 84 years with a mean age of 49 have educational backgrounds ranging from four to twenty years. Participants were grouped into categories based on their sex, age and education. All test procedures were explained and a written consent was obtained from each of them. All the tests were administered based on standard protocols (Oxford Project To Investigate Memory and Ageing [OPTIMA], Cambridge Mental Disorders of the Elderly Examination (CAMDEX) and CUPTIMA).

2.2. Methods

The 7-min screen test was developed to test cognitive impairment especially dementia prone Alzheimer's disease. The various tests coming under this are orientation test, memory test, clock drawing test and verbal fluency test. The scores obtained from all the above tests were then analyzed using the scoring calculator, to find out the probability of dementia related problems.[16] Serum calcium, magnesium and phosphorus were estimated with their respective slide by Johnson and Johnson fully automatic analyzer (Vitros FS 5.1, Johnson and Johnson).

2.3. Statistical analysis

The data of biochemical test parameters were analyzed with SPSS software version 17. The following statistical tests were conducted for analysis, which include ANOVA, Independent sample test and Pearson correlation.

3. Results

The 7-min screen test was administered in all the age groups and found an increasing trend in the score as age advanced (Table 1). Orientation score in younger age group was compared with older age groups. A statistically significant difference was found between younger age group (20–29) and other groups ($p < 0.05$). One way ANOVA was conducted between the groups and within the groups and a mean square value of 52.847 and 0.518 respectively with a highly significant p value (< 0.001) was observed. The score in male was 1.4 ± 1.14 and in female was 1.58 ± 1.266. No statistically significant difference was observed between the scores in male and female ($p = 0.171$).

It was also found that when the education level increased the orientation score decreased. A statistically significant difference was observed between the highly educated and the uneducated in the Orientation test score ($p < 0.001$). In primary educated group, the value was 2.02 ± 1.10, in the secondary educated group, the value was 1.23 ± 1.16 but in the tertiary educated group, it was 0.98 ± 1.11. The values were statistically highly significant ($p < 0.001$).

Memory test was administered in all the age groups and was found to have a decreasing trend in the score as age advances. Memory test in younger age group (20–29) was

Table 1 Mean 7-min screen test score in different age groups, education category and sex of participants.

		Orientation		Memory		Clock drawing		Verbal fluency	
Age	N	M	SD	M	SD	M	SD	M	SD
7 min screen test									
Age group									
20–29	60	0.35	0.481	15.6	0.527	6.37	0.736	23.15	2.441
30–39	58	0.71	0.726	15.34	0.637	6.28	0.951	22.93	2.937
40–49	57	1.07	0.799	15.09	0.714	6.02	0.896	22.35	2.949
50–59	52	1.56	0.873	14.92	0.652	5.75	1.118	21.35	2.424
60–60	48	2.17	0.859	14.73	0.644	5.33	1.294	20.00	2.642
70–79	43	2.81	0.588	14.28	0.908	4.51	1.162	17.60	2.331
⩾80	19	3.74	0.452	12.63	0.895	3.47	0.513	13.63	1.342
Total	337	1.48	1.205	14.91	0.971	5.65	1.273	21.01	3.618
Educational group									
Primary	129	2.02	1.104	14.52	0.985	5.17	1.347	19.47	3.300
Secondary	144	1.23	1.163	15.06	0.937	5.85	1.202	21.38	3.363
Tertiary	64	0.98	1.105	15.34	0.718	6.17	0.918	23.28	3.402
Total	337	1.48	1.205	14.91	0.971	5.65	1.273	21.01	3.618
Sex group									
Male	174	1.40	1.142	15.10	0.802	5.78	1.245	21.48	3.523
Female	163	1.58	1.266	14.70	1.089	5.52	1.293	20.50	3.661

15.6 ± 0.53, and in 80 and above age group it was 12.63 ± 0.90. A statistically significant difference was found between younger and older age groups ($p < 0.001$). Mean square value from one way ANOVA revealed a highly significant change ($p < 0.001$) between the groups and within the groups (26.442 and 0.48 respectively). The score of male and female was compared and the values were 15.1 ± 0.802 and 14.7 ± 1.089 respectively. A statistically significant difference was observed between the scores in male and female ($p < 0.001$). A statistically significant difference was observed between the highly educated participants and the uneducated in the memory test score ($p < 0.001$). In primary educated group, the value was 14.52 ± 0.99, in secondary, it was 15.06 ± 0.94, but in tertiary educated group, it was 15.34 ± 0.71. Statistically the values were highly significant ($p < 0.001$).

The clock drawing test was administered in all the participants and correlated. The result showed a decreasing trend as age advances. In the younger age group (20–29) the value was 6.37 ± 0.74; however, the value in subjects above 80 years was 3.47 ± 0.51. One way ANOVA revealed a statistically significant difference ($p < 0.001$) between the groups and within the groups with a mean square value of 35.38 and 1.007. The score was found to be increased as the education level advanced. The score of male was 5.78 ± 1.25 and for female it was 5.52 ± 1.29. A statistically significant difference was observed between the scores in male and female ($p = 0.06$). A statistically significant difference was observed between the highly educated participants and the uneducated in the clock drawing test score ($p < 0.001$). In the primary educated group, the value was 5.17 ± 1.35, in the secondary educated group, it was 5.85 ± 1.20, but in the tertiary educated group it was 6.17 ± 0.92. Statistically the values were highly significant ($p < 0.001$).

Verbal fluency (Semantic category) test was administered in all the participants and it was found a decreasing trend in the score as age advances. Verbal fluency test in younger age group was compared with all other groups. One way ANOVA revealed a statistically significant difference ($p < 0.001$) between younger age and the older age groups with a mean square value between the groups and within the groups with a value of 363.19 and 6.72 respectively. It was found that as the education level increased the verbal fluency score also increased. A statistically significant difference was observed between the subjects with higher education level and those with lower education level. In subjects who completed tertiary level of education, the score was found to be higher than the primary educated group. The scores in the tertiary educated group and uneducated primary group were compared and found to be statistically significant ($p < 0.001$), which shows that there is cognitive impairment in uneducated and elderly participants. The verbal fluency test in male and female was also compared. The score in male and female was 21.48 ± 3.52 and 20.5 ± 3.661 respectively. Statistically significant difference was observed between the scores of males and females ($p < 0.001$).

Based on the 7-min screen test, probability of dementia in the different age groups was also calculated. The participants with 75.81 ± 6.93 age ($n = 43$) showed high probability to dementia (HI) than the lower age group 'LO' (44.33 ± 16.56, $n = 286$). A statistically significant difference in dementia probability was observed between the higher and lower age groups ($p < 0.001$) (Table 2), of which eight subjects were rechecked (RE). Among HI dementia probability with Alzheimer's characteristics, 39.5% was male and 60.5% was female. However, we got an interesting finding that as the status of education increased the chances of dementia with characteristics of Alzheimer's disease decreased ($p < 0.001$) (Table 3).

Out of these selected participants, 37.5% belonged to HI group, 37.5% belonged to LO group and remaining 25% belonged to RE group based on the 7-min screen test. All the participants were well matched for age and sex. A number of cognitive assessment tests were used to evaluate cognitive function in this population and a composite score was created

Table 2 Dementia probability in different age groups (descriptive).

	N	Mean age	SD	95% Confidence interval for mean	
				Lower bound	Upper bound
Dementia probability of Alzheimer's characteristics					
HI	43	75.81	6.929	73.68	77.95
LO	286	44.33	16.564	42.4	46.26
RE	8	67.75	5.12	63.47	72.03
Total	337	48.91	18.926	46.88	50.93

to represent cognitive function/impairment. Descriptive statistics for each biochemical test parameters are presented in Table 4.

Serum Mg was estimated in all the participants. In the dementia probability LO group, the mean serum Mg was 2.06 ± 0.25 and in the HI group it was 1.36 ± 0.14. One way ANOVA was conducted between the groups and within the groups which showed a highly significant change. Between the groups the mean square value was 1.566 with a p value of <0.001 and within the groups the value was 0.034 with a p value of <0.0031 (Fig. 1).

Serum Ca was estimated in all the participants. In the dementia probability LO group, the mean serum Ca was 10.55 ± 0.51 and in the HI group it was 8.97 ± 0.26. One way ANOVA was conducted between the groups and within the groups, which showed a highly significant change. Between the groups, the mean square value was 8.19 with a p value of <0.001 and within the groups the value was 0.17 with a p value of <0.001 (Fig. 2).

Serum P was estimated in all the participants. In the dementia probability LO group, the mean serum phosphorus was 2.70 ± 0.19 and in the HI group it was 4.00 ± 0.54. One way ANOVA was conducted between the groups and within the groups which showed highly significant changes. Between the groups, the mean square value was 5.16 with a p value of <0.001 and within the groups the value was 0.16 with a p value of <0.001(Fig. 3).

4. Discussion

Macronutrients are chemical elements that are needed for the proper growth, development and physiology of the organism. Macronutrients are routinely involved in metabolic processes and oxidation–reduction reactions in the CNS and could have a possible effect on cognitive function.

All the three macronutrients that we estimated (calcium, magnesium and phosphorus) were found to be significantly related to the composite cognitive score. Increasing plasma calcium and magnesium level was associated with higher cognitive score ($p < 0.0001$). Increasing phosphorus, in contrast, was significantly associated with lower composite score. The relationship between trace elements measured in dietary intake or in drinking water and cognitive function in elderly persons has been examined previously and calcium levels in drinking water have a positive association with cognitive function.[17–19]

In this sample of our elderly participants, we found a significant association between increased plasma calcium and magnesium levels and higher cognitive function scores. We also identified plasma phosphorus level as a factor associated with lower cognitive scores. The mechanisms between the association of micro, macronutrients and brain functions are thought to be through impact on neurotransmitting processes, oxygenation in the cerebral parenchyma, in the synthesis of neurotransmitters and in the formation of calcification in the brain. Another study in women showed that Alzheimer's patients had lower serum calcium levels compared to non-demented women.[20] The mechanism for calcium's impact on brain function is hypothesized to be that, increased calcium level enhances brain dopamine synthesis through a calmodulin-dependent system and increased dopamine levels regulate various brain functions.[21]

The association between plasma phosphorus level and cognitive score, we report in this study, is consistent with previous findings[22], where the mechanism for phosphorus and its impact on cognition is believed to be its interaction with calcification in the basal ganglia, thalamus and cerebral white matter, which is associated with cognitive impairment. In another study[23] it was observed that a decreased serum phosphorus reduced arterial stiffness and improved cognitive function and renal disease. The mean phosphorus level in our 'HI' sample (4 mg/dL) was slightly higher than the mean plasma phosphorus level reported in 'LO' participants (2.7 mg/dL).

Magnesium plays a vital role in neurochemical transmission and therefore its deficiency has been related to a number of disorders of the central nervous system. The water-soluble vitamins (B group and C), together with the minerals, calcium, magnesium and zinc are most relevant for cognitive performance.[24] Clinical evidence revealed that marginal deficiencies

Table 3 Dementia probability in different education category and sex (crosstab).

	Educational level				Sex		
	Primary	Secondary	Tertiary	Total	Male	Female	Total
Dementia characteristic of Alzheimer's disease							
HI	27	13	3	43	17	26	43
	62.80%	30.20%	7.00%	100.00%	39.5%	60.5%	100%
LO	97	129	60	286	153	133	286
	33.90%	45.10%	21.00%	100.00%	53.5%	46.5%	100.0%
RE	5	2	1	8	4	4	8
	62.50%	25.00%	12.50%	100.00%	50.0%	50.0%	100%
Total	129	144	64	337	174	163	337
	38.30%	42.70%	19.00%	100.00%	51.6%	48.4%	100.0%

Table 4 Mean serum magnesium, calcium and phosphorus values in different categories (mg/dL).

	Magnesium			Calcium			Phosphorus		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Dementia probability									
HI	1.358	0.1443	0.042	8.967	0.264	0.0762	4	0.5377	0.1552
LO	2.058	0.2539	0.073	10.55	0.5143	0.1485	2.7	0.1859	0.0537
RE	1.888	0.0835	0.03	9.288	0.4324	0.1529	3.175	0.4062	0.1436
Total	1.753	0.3645	0.064	9.641	0.83	0.1467	3.306	0.6965	0.1231

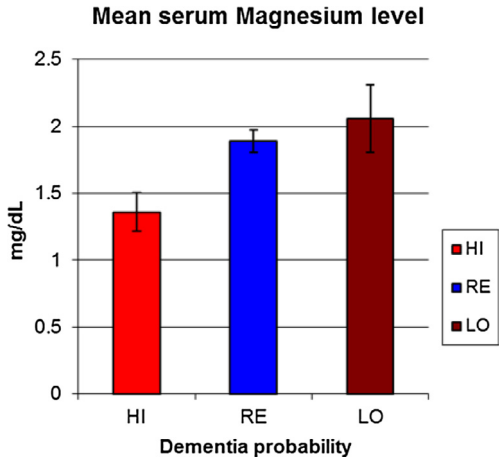

Figure 1 Mean serum level of magnesium in different categories of participants.

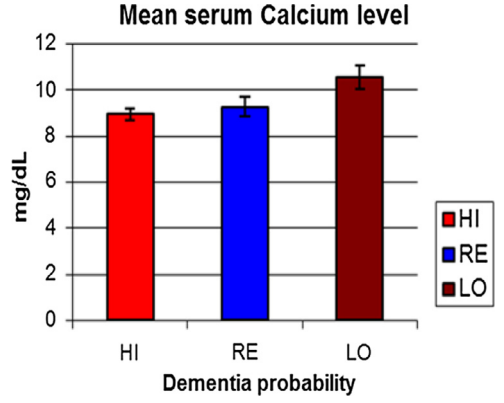

Figure 2 Mean serum level of calcium in different categories of participants.

of one or more of these micronutrients are common, even in the developed countries and that, such deficiencies may affect cognitive performance, especially in vulnerable groups such as the elderly and those individuals who are exposed to occupational pressures and a stressful lifestyle.[25] Magnesium is also crucial to many functions of cell metabolism. In patients with Alzheimer's disease, increased severity of cognitive impairment is significantly associated with lower levels of serum magnesium[26] and in hypertensive patients, reduced cognitive performance has also been associated with lower magnesium level.[27]

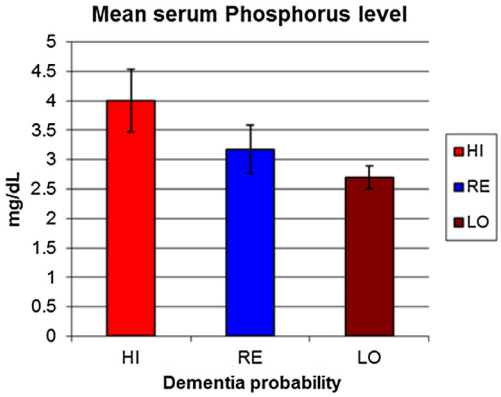

Figure 3 Mean serum level of phosphorus in different categories of participants.

A review of the literature on magnesium and dementia suggests that magnesium supplementation could have neuroprotective effects in aging and specifically in dementia patients and is already shown to facilitate learning and memory performance.[28]

In an animal study it has been observed that an increase in brain magnesium improves learning and memory in young and old rats and suggests that increasing magnesium intake may be a valid strategy to enhance cognitive abilities and supports speculation that inadequate levels of magnesium impair cognitive function, leading to faster deterioration of memory in aging humans. Diet can have a significant impact on cognitive capacity. Identification of dietary factors which have a positive influence on synapses, the sites of communication between neurons, might help to enhance learning and memory and prevent their decline with age and disease. It is observed that magnesium is essential for the proper functioning of many tissues in the body, including the brain and demonstrated that magnesium promoted synaptic plasticity in cultured brain cells and boost brain power.[29] It is also found that increased brain magnesium enhanced many different forms of learning and memory in both young and aged rats. A close examination of cellular changes associated with memory revealed an increase in the number of functional synapses, activation of key signaling molecules and an enhancement of short- and long-term synaptic processes that are crucial for learning and memory. A recent study on animals[30] showed that elevating brain magnesium was effective at preventing/reversing learning and memory deterioration in transgenic (Tg) mice.

Elevation of brain magnesium was effective at restoring synapse density at the end stage of AD-like pathological

progression in Tg mice, which might be responsible for the restoration of cognitive functions.

5. Conclusion

The results of our study give us an expression that macronutrients such as calcium, magnesium and phosphorus may be associated with cognitive function in elderly population. Calcium and magnesium are associated with cognitive improvement in elderly, but in contrast, higher level of phosphorus facilitates cognitive decline. But further studies on a large population are required to come out with a definite conclusion. Our findings suggest that elevating brain magnesium content via increasing magnesium intake might be a useful new strategy to enhance cognitive abilities. Moreover, half the population of industrialized/developing countries have magnesium deficit, which increases with aging. This may very well contribute to age-dependent memory decline; increasing magnesium intake might prevent or reduce such decline in memory. Our results demonstrate the existence of a significant association between magnesium imbalance and cognitive impairment.

Conflict of interest

None. All the study participants had given their informed written consent and study was approved by Human ethical committee.

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