ORIGINAL ARTICLE

The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial

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Background: Nearly 50% of older adults have insomnia, with difficulty in getting to sleep, early awakening, or feeling unrefreshed on waking. With aging, several changes occur that can place one at risk for insomnia, including age-related changes in various circadian rhythms, environmental and lifestyle changes, and decreased nutrients intake, absorption, retention, and utilization. The natural *N*-methyl-D-aspartic acid (NMDA) antagonist and GABA agonist, Mg^{2+}, seems to play a key role in the regulation of sleep. The objective of this study was to determine the efficacy of magnesium supplementation to improve insomnia in elderly. **Materials and Methods:** A double-blind randomized clinical trial was conducted in 46 elderly subjects, randomly allocated into the magnesium or the placebo group and received 500 mg magnesium or placebo daily for 8 weeks. Questionnaires of insomnia severity index (ISI), physical activity, and sleep log were completed at baseline and after the intervention period. Anthropometric confounding factors, daily intake of magnesium, calcium, potassium, caffeine, calories form carbohydrates, and total calorie intake, were obtained using 24-h recall for 3 days. Blood samples were taken at baseline and after the intervention period for analysis of serum magnesium, renin, melatonin, and cortisol. Statistical analyses were performed using $SPSS_{19}$ and P values < 0.05 were considered as statistically significant. **Results:** No significant differences were observed in assessed variables between the two groups at the baseline. As compared to the placebo group, in the experimental group, dietary magnesium supplementation brought about statistically significant increases in sleep time ($P = 0.002$), sleep efficiency ($P = 0.03$), concentration of serum renin ($P < 0.001$), and melatonin ($P = 0.007$), and also resulted in significant decrease of ISI score ($P = 0.006$), sleep onset latency ($P = 0.02$) and serum cortisol concentration ($P = 0.008$). Supplementation also resulted in marginally between-group significant reduction in early morning awakening ($P = 0.08$) and serum magnesium concentration ($P = 0.06$). Although total sleep time ($P = 0.37$) did not show any significant between-group differences. **Conclusion:** Supplementation of magnesium appears to improve subjective measures of insomnia such as ISI score, sleep efficiency, sleep time and sleep onset latency, early morning awakening, and likewise, insomnia objective measures such as concentration of serum renin, melatonin, and serum cortisol, in elderly people.

Key words: Dietary supplementation, elderly, insomnia, magnesium

INTRODUCTION

Insomnia is a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final wakening. Insomnia is not necessarily an inevitable consequence of aging, but its prevalence increases with age [1,2] and most elderly people who have not appropriate geriatric conditions, may suffer from major sleep disorders.[3] In other words, aging itself does not lead to sleep disorders, and this problem is due to other factors associated with aging.[4] The most important age-related sleep changes include decreased sleep duration, decreased sleep efficiency (SE) (the percentage of sleeping time after going to bed), and decreased short-wave sleep, which all are categorized as insomnia.[5,6] The prevalence of insomnia in all population groups is between 10% and 48%.[1] One population survey of insomnia prevalence in the elderly found that 42% of participants reported difficulty initiating and maintaining sleep. Following up, the results of the study for 3 years found that 15% of contributors who did not reported insomnia had disturbed sleep, suggesting an annual incidence rate of approximately 5 percent.[2] In other statistics, the insomnia is estimated to be present in 40-50% percent of elderly people above 60 years of age.[7]

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In all age groups, the individuals who suffer from insomnia show memory weakness, increased reaction time, short-term memory problems, and lowered efficacy level. However, insomnia is more problematic in elderly subjects, because it puts them at higher risk for falling, cognitive impairments, weak physical function, and mortality (from 1.3 to 3 times higher than normal subjects).[8-10] Sleep disorders are also related to decreased quality of life and general health and increased health costs, stress, and depression symptoms.[11]

Currently, insomnia treatment includes medicinal and nonmedicinal treatments. Regarding the effects of nonmedicinal methods in insomniac individuals, there are low or medium quality evidences, or no important clinical results. In general, there is no precise information about the beneficial effects of these methods on insomnia treatment compared to control groups.[12] Medicinal treatment of insomnia is done through a broad spectrum of drugs; however, Sleep Disorders Conference of American National Institutes of Health has declared that drugs used routinely for treatment of sleep disorders have more hazards than benefits and are not recommended for elderly.[13] Particularly, there is a concern about elderly people, since 81% of hypnotic drugs are used in daily and long-term patterns by them.[14]

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. It is involved in more than 300 biochemical reactions of the body.[15] Magnesium is an essential cofactor for many enzymatic reactions, especially those that are involved in energy metabolism and neurotransmitter synthesis.[16] Aging is a major risk factor for magnesium deficiency. Numerous changes are occurring in magnesium status during elderly. Its total level reduces due to a decrease in bone mass which is the most important magnesium source in the body. Epidemiologic studies show that despite important physiologic role of magnesium, its dietary intake is inadequate in various societies,[17-20] and some population groups, especially elderly people have low magnesium intake,[17-25] which can be due to inability in using magnesium sources or their tendencies to consume more processed food and less whole grains and green leafy vegetables. However, it is shown that magnesium requirements do not change by aging.[25] Other alterations in magnesium metabolism, which are related to aging, are reduced magnesium intake, reduced intestinal uptake, increased urinal and fecal excretion, and drug induced.[16, 26] Meanwhile, it seems that reduced magnesium intake has the most important role in age-related magnesium deficiency.[26] Dietary magnesium deficiency in the elderly is much higher than expected and its intake decreases continuously and exponentially with age, independent of gender and race.[21] NHANCES III analysis shows that elders' magnesium intake in United States is much less than recommended dietary allowance (RDA) and compared to recommended levels of 420 and 320 mg/day, respectively for men and women, is equal to 225 mg/day for men and 166 mg/day for women. Yet, little is known about the magnesium status in Iran, especially in elderly population. The only well-designed population-based survey in Iran of dietary magnesium intake was conducted from 1999 through 2001 (within the framework of the Tehran Lipid and Glucose Study). A striking result of an analysis of that survey was the lower mean magnesium intake among participants. In aforementioned study, 95% of subjects failed to meet magnesium requirements (137 ± 28 mg/day).[27]

Although the effect of magnesium on neural function and sleep behaviors is not fully understood, magnesium has an essential role in ion channels conductivity, such as *N*-Methyl-D-aspartic acid (NMDA) receptor, and unilateral entrance of potassium channels. In addition, magnesium is essential for connection of monoamines to their receptors. Thus, this cation has a key role in neural transmission at cellular level, both in presynaptic membrane and postsynaptic membrane. Several studies have also acknowledged the role of magnesium in the regulation of central nervous system excitability.[28] Therefore, magnesium as a natural antagonist of NMDA and agonist of GABA seems to play a critical role in sleep regulation.

According to mentioned issues, if magnesium supplementation can prevent insomnia side effects through its improvement, it can be used as an alternative treatment of routine drugs or in combination with them in order to reduce their numerous side effects. For this purpose, the present study is conducted to determine the impact of magnesium supplementation on insomnia in elderly.

MATERIALS AND METHODS

Subjects

Based on evidences in the literature[29-32] and regarding to Held *et al*. study,[31] concentration of serum renin was chosen to estimate the sample size. Serum renin concentration was expected to have 0.6 mIU/ml difference between placebo and supplementation groups. A sample size of 21 participants per group has 80% power to detect such a difference and a significance level of 5%. To adjust for an expected drop-out rate of 10%, approximately 46 participants (23 per group) needed to be enrolled in the study. So subjects consisted of 46 volunteers, (23 women, 23 men; age 65 ± 4.6) who entered the study after passing through psychiatric examinations and insomnia severity index (ISI) test, in order

to confirm their primary insomnia (clinically moderate or severe), and their sleep time (ST) was registered in sleep log forms for 14 days, prior to begin supplementation (run-in phase). Investigators assigned consecutive code numbers to participants from a prespecified list. Simple sampling method was used to select patients who were then randomly allocated into the magnesium or the placebo group and received 500 mg elemental magnesium or placebo daily for 8 weeks. For those who were consistent with inclusion criteria and lacked the exclusion criteria of the study, the benefits, the aim, and duration of the study, and mode of intervention were described in a briefing. Criteria for inclusion in our double-blind randomized clinical trial included: Willing to cooperate, age 60-75 years, having insomnia according to ISI and sleep-log questionnaires, having body mass index (BMI) range of 25-34.9, dietary intake of magnesium under 75% RDA; serum magnesium level under 0.95 mmol/L, not receiving loop diuretics, cyclosporine, digoxin, amphotericin and any hormonal treatment, not having renal diseases, acute heart failure, sleep-related movement disorders (such as restless leg syndrome), and sleep-related respiratory disorders (such as sleep apnea). Reasons for exclusion from the study were: Psychiatric disorder history, recent stressful life events (e.g., divorce or death or acute illness of a family member), substance or alcohol abuse, and a transmeridian flight during last 6 weeks. Written informed consent was obtained from all subjects. The study was approved by ethics committee of Shahid Beheshti University of Medical Sciences.

Study design and measurements

The study was performed in a double-blind randomized placebo-controlled parallel design, in January to March 2012 in Health Divisions of Cultural Centers of Tehran's 1, 10, and 14 districts. Magnesium was administered as magnesium oxide tablets twice a day (each tablet containing 414 mg magnesium oxide as 250 mg elemental magnesium) for 8 weeks. Questionnaires of ISI, physical activity, and sleep log were completed at baseline and after the intervention period. Anthropometric confounding factors, daily intake of magnesium, calcium, potassium, caffeine, calorie form carbohydrates, and total calorie intake, were obtained using 24-h recall for 3 days.

To analyze biochemical factors of contributors, they were asked to be fasted for 12 h. Then venous blood samples were collected by a trained nurse and cooled rapidly to 2°C, then within 2-3 h, the blood samples were centrifuged with 3500 g velocity for 15 min and the sera were put in a –80°C freezer. The serum magnesium level was measured through atomic absorption spectrometry method and its cortisol, renin, and melatonin levels were measured through ELISA method. After collecting biochemical samples, anthropometric measurements were done by trained colleagues; so, according to WHO standards, the light cloth worn patients were weighted and their height were measured without shoes with a 0.5 cm accuracy wall meter. Using the weight (in kilograms) divided by height (in meters) square formula, BMI was calculated and the obtained information was recorded in general information questionnaire of patients. These measurements were repeated at the end of eighth week of the study.

Statistical methods

Quantitative variables were expressed as mean ± standard deviation. All variables were tested for normality by the Kolmogorov–Smirnov test before any statistical comparisons were made, then if their distribution were normal in the population, to compare the quantitative variables and their mean in each group the paired *t*-test, and to compare their mean between two groups, the independent samples *t*-test were used. If the distribution was not normal, to compare within the groups, Wilcoxon test was used and to compare between the groups Mann-Whitney test was used.To compare the qualitative confounding variables between two groups, Chi-square test was used. Statistical analyses were performed using SPSS software version 19 and P values < 0.05 were considered as statistically significant. Also $0.05 < P$ values < 0.1 were reported as marginally significant.

RESULTS

Of 46 persons participating in the study, 2 persons due to not regular consumption of supplement or placebo and 1 person due to not participating in second turn blood sampling were excluded from the study. At the end, 43 persons (21 men and 22 women) completed the study. The age, weight, height, and BMI means and standard deviations of contributors were 65 ± 4.6 years (control: 65.4 ± 4.5; intervention: 64.7 ± 4.7), 72.1 ± 9.7 kg) control: 73.1 ± 9.5; intervention: 71 ± 10), 157 ± 8.1 cm (control: 156 ± 6.4; intervention: 158.5 ± 9.5), and 29.2 ± 3.7 kg/m^2) control: 30.11 ± 4.1; intervention: 28.23 ± 3.11), respectively.

The dietary intakes of the study participants at the baseline and end of the study are shown in table 1. During the study, the dietary intake of individuals in none of investigated micronutrients and caffeine intake showed no significant statistical difference. In this study the changes of weight ($P = 0.07$) and BMI ($P = 0.07$) between two groups were not significant. Physical activity level ($P = 0.02$) in magnesium supplement group compared to placebo group showed a significant increase, which based on literature is presumed to be related to the fact that improvement in sleep patterns through decrement of daytime fatigue and

sleepiness and their related high risk behaviors, results in increment of daily physical activity level.[33-35]

Table 2 summarizes sleep indices evaluations. As compared to the placebo group, in the experimental group, dietary magnesium supplementation brought about statistically significant increases in ST (P = 0.002) and SE (P = 0.03). Also sleep onset latency (SOL) (P = 0.02) and early morning awakening (EMA) (P = 0.08) decreased significantly and marginally significant, respectively. However, total sleep time (TST) (P = 0.37) did not show any significant differences between two groups. In addition, the obtained ISI (P = 0.006) from ISI questionnaire revealed a significant decrease between two groups, in statistical terms [Table 2].

At the beginning of the study, no significant difference was seen in serum concentrations of investigated biochemical indices between two groups. The mean of changes of fasting magnesium, renin, cortisol, and melatonin levels were compared between two groups receiving magnesium supplement and placebo, via independent t-test. As compared to the placebo group, in the experimental group, the serum renin (P < 0.001) and melatonin (P = 0.007) levels showed a significant increase and serum cortisol level (P = 0.008) showed a significant decrease [Table 3]. Despite favorable increase of serum magnesium level during this study, the related changes in its level were just marginally significant (P = 0.06). Table 4 also shows the effect of magnesium supplementation or placebo on percent change of subjective and objective measures of insomnia in control and experimental groups.

Table 1: Means and standard deviations of dietary confounding factors in magnesium supplementation and placebo groups at baseline

Variable (mg/day)	Magnesium supplementation	Placebo	*P*
Dietary magnesium intake	190±55	198±54	0.970
Dietary calcium intake	829±317	795±365	0.743
Dietary potassium intake	3006±897	2996±772	0.970
Dietary caffeine intake	77±43	69±29	0.475

P value<0.05 is considered as significant

DISCUSSION

This double-blind, placebo-controlled clinical trial is the first study to the knowledge of the authors, to survey the interdependent role of magnesium in treatment of insomnia and to show that magnesium supplementation results in significantly improvement of subjective and objective measures of insomnia than a placebo treatment in elderly people experiencing primary insomnia. The benefits of this supplementation in primary insomnia, in elderly subjects, appear to have significant clinical importance because insomnia is common in late life, which if left untreated may have clinical, economic, and human consequences for the individual and society.[25,36]

Magnesium is an essential element that is crucial to hundreds of physiologic processes in humans. Not surprisingly, inadequate intake of magnesium has been

Table 2: Comparison of sleep indices in magnesium supplementation and placebo groups before and after intervention

Variable	Magnesium supplementation (*n*=21)			*P*1*	Placebo (*n*=22)			*P*2†	*P*3‡
	Before intervention	After intervention	Difference (CI=95%)		Before intervention	After intervention	Difference (CI=95%)		
Insomnia severity index	16.52±2.01	14.14±2.68	−2.38±2.24	<0.001	16.27±1.69	15.77±1.92	−0.5±1.71	0.2	0.006
Total sleep time (h)	7.8±1.1	7.9±0.6	0.1±0.7	0.4	7.6±0.9	7.6±0.8	−0.03±0.3	0.6	0.3
Sleep time (h)	5.1±0.8	5.7±0.9	0.6±0.7	0.002	5.0±0.5	5.0±0.6	−0.02±0.3	0.7	0.002
Sleep onset latency (h)	1.3±0.2	1.1±0.4	−0.2±0.4	0.04	1.4±0.2	1.4±0.2	0.04±0.1	0.1	0.02
Early morning awakening (h)	1.04±0.02	1.01±0.05	−0.03±0.05	0.05	1.03±0.02	1.03±0.02	−0.01±0.01	0.09	0.08
Sleep efficiency (h)	0.67±0.07	0.73±0.1	0.06±0.1	0.02	0.66±0.04	0.66±0.07	0.00±0.05	0.2	0.006

*P*1* *P* value of differences in magnesium group compared via paired *t*-test; *P*2† *P* value of differences in placebo group compared via paired *t*-test; *P*3‡ *P* value of differences between magnesium and placebo groups compared via independent samples *t*-test

Table 3: Comparing serum magnesium and biochemical indices of circadian cycle in magnesium supplementation and placebo groups before and after intervention

Variable	Magnesium supplementation (*n*=21)			*P*1*	Placebo (*n*=22)			*P*2†	*P*3‡
	Before intervention	After intervention	Difference (CI=95%)		Before intervention	After intervention	Difference (CI=95%)		
Serum magnesium (mmol/l)	0.83±0.06	0.86±0.05	0.03±0.07	0.08	0.82±0.07	0.81±0.07	−0.01±0.07	0.38	0.06
Serum renin (mIU/ml)	18.49±8.02	24.40±11.2	5.91±7.49	0.002	18.55±8.2	17.54±8.3	−1.00±2.57	0.08	<0.001
Serum melatonin (pg/ml)	9.31±6.26	10.90±6.85	1.58±2.97	0.02	9.55±4.74	8.12±3.27	−1.43±3.90	0.1	0.007
Serum cortisol (μg/dl)	23.05±6.41	20.46±6.24	−2.59±6.05	0.03	21.61±6.04	22.25±6.07	0.63±1.89	0.1	0.008

*P*1* *P* value of differences in magnesium group compared via paired *t*-test; *P*2† *P* value of differences in placebo group compared via paired *t*-test; *P*3‡ *P* value of differences between magnesium and placebo groups compared via independent samples *t*-test

Table 4: Percent change in subjective and objective measures of insomnia in participants, after 8 weeks of supplementation as compared with controls

Parameter	% Change over baseline*	
	Supplement	Placebo
Insomnia severity index	−14.4 (−31.6, 2.8)[a,b]	−2.7 (−7.2, 1.6)
Total sleep time (h)	3 (−1.8, 7.6)	−0.19 (−2.3, 1.9)
Sleep time (h)	12 (5.2, 18.9)[a,b]	−0.27 (−2.7, 2.2)
Sleep onset latency (h)	−14 (−30.8, 2.7)[a,b]	3.7 (−1.0, 8.4)
Early morning awakening (h)	−3 (−5.1, −0.8)[a]	−1.0 (−1.7, −0.3)
Sleep efficiency (h)	9.6 (2.5, 16.7)[a,b]	0.1 (−2.9, 3.1)
Serum magnesium (mmol/l)	4.2 (−0.2, 8.5)	−1.3 (−5.5, 2.9)
Serum renin (mIU/ml)	36.7 (18.2, 55.2)[a,b]	−5.9 (−13.8, 1.9)
Serum melatonin (pg/ml)	35 (10.5, 59.5)[a,b]	−1.1 (−23.6, 21.3)
Serum cortisol (μg/dl)	−8.2 (−19.6, 3.1)[a,b]	3.5 (−0.48, 7.6)

[a]% change over baseline significant ($P<0.05$); [b]% change over baseline significantly higher than control ($P<0.05$); *Figures in parentheses show 95% confidence interval for mean

linked to various adverse health outcomes, including sleep disorders. Despite the physiologic role of magnesium and its proven or potential benefits, epidemiologic surveys show that the dietary intake of magnesium is inadequate in various populations.[17-20,27] The findings of magnesium intake below recommendations by many raise the issue of the adequacy of magnesium status in population.[21] Yet, little is known about the magnesium status in Iran, especially in elderly population. The only well-designed population-based survey in Iran of dietary magnesium intake was conducted from 1999 through 2001 (within the framework of the Tehran Lipid and Glucose Study). A striking result of an analysis of that survey was the lower mean magnesium intake among participants. In aforementioned study, 95% of subjects failed to meet magnesium requirements (137 ± 28 mg/day).[27] Some population groups, such as the elderly, have particularly lower magnesium intake than reference groups[17,22] and aging is a major risk factor for magnesium deficiency. Dietary habits, nutrient intakes and aging processes are interrelated and are of particular importance among the elderly.[37] Numerous changes occurred in magnesium status during elderly. Its total level reduces due to a decrease in bone mass which is the most important magnesium source in the body. Also, lower magnesium intake may occur due to inability in using magnesium sources or their tendencies to consume more processed food and less whole grains and green leafy vegetables. Other alterations in magnesium metabolism, related to aging, are reduced intestinal uptake, increased urinal and fecal excretion, and drug induced.[16,26] Meanwhile, it seems that reduced magnesium intake has the most important role in age-related magnesium deficiency.[26] Nuts, seeds and beans, whole grains, and fish and seafood are the best sources of magnesium in the diet. In addition to the above foods, dark green leafy vegetables are good sources of magnesium.[37] Several studies have suggested that the effect of age on dietary habits may be attributable to functional impairments[38,39] and chewing problems.[40,41] Reduced functional capacity might have a large influence on food choice and, as a consequence, on nutrient intake — especially magnesium, regarding to its dietary sources — in old age. Older people chose different foods, suggesting that older persons tend to adapt their diet to the functional difficulties that often occur during the aging process. These factors may lead elderly persons to have a monotonous and energy-restricted diet, which easily results in an inadequate intake of nutrients.[42]

There are a limited numbers of epidemiologic studies, of sufficient size that have assessed magnesium status in the elderly population, which makes it difficult to make specific recommendations on magnesium intakes in subgroups of older persons. But review of findings of previous studies suggests that treatment of potential physical and functional problems, increasing consumption of magnesium sources such as nuts, seeds and beans, whole grains and dark green leafy vegetables and increasing the dietary diversity — which is associated with diet quality —[37] within the context of a diet that maintains the appropriate energy balance and if required, magnesium supplementation, might be a good recommendation for this population to meet their requirements.

The results of our study showed that ST ($P = 0.002$) and SE ($P = 0.03$) increased and SOL ($P = 0.02$) decreased, both significantly. However, TST ($P = 0.37$) and EMA ($P = 0.08$) did not show a significant difference. In addition, the obtained ISI ($P = 0.006$) from ISI questionnaire revealed a significant decrease. Results of the present study about the role of magnesium in sleep regulation are consistent with *Dralle* and *Bodeker* study, which showed that there is an association between magnesium supplementation and REM, muscle tone, and gross body movements in infants. Results of *Dralle* and *Bodeker* also suggested that there is a relationship between serum magnesium level and active sleep, likewise between serum magnesium level and quiet sleep. In their study magnesium supplementation increased the quiet sleep and decreased the active sleep.[29] Also, the results of our study are consistent with *Murck* and *Steiger* study in which the most important effects of Mg^{2+} supplementation were an increment in spindle power during non-rapid eye movement (NREM) and a change in delta power in the in the third sleep cycle.[30] In a study conducted by *Held et al.* to analyze magnesium supplementation effects on sleep EEG, plasma ACTH, cortisol, AVP, renin, angiotensin II, and aldosterone in elderly, which showed that the most important Mg^{2+} supplementation effect in healthy elderly subjects was short wave sleep (SWS) increment.[31] Also, the results of

our study are consistent with *Rondanelli et al.* study, which was done to investigate the effects of combined melatonin, magnesium, and zinc supplementation, which showed that the supplementation resulted in total score improvement of Pittsburg questionnaire compared to placebo, and suggested that treatment has beneficial effects on capability of recovering body activities through sleep.[32]

In the present study, regarding to increase in SE — as the best total scale of insomnia[43] — from 0.63 to 0.73 in supplement group, it can be concluded that despite lack of change in TST of each person, if ST and adequacy of sleep increased and SOL decreased, in the same range, there is no need to increase TST in order to relieve the fatigue caused by daily activities and to recover body's ability through sleep.

In the present study, serum magnesium level in supplement group tended to augment ($P = 0.06$); however, difference between two groups was just marginally significant at the end of the study. The method used for magnesium status assessment in the present study was the measurement of serum magnesium concentration. Since 99% of magnesium is in the bone and soft tissue, clinical assessment of magnesium status is difficult and has become now a challenge for clinical laboratories.[44] Based on the observations of several investigations, currently serum magnesium analysis appears to be the most practical, accessible, and expeditious method of identifying changes in magnesium homeostasis.[45] The obtained results from our study are consistent with the study of *Hoogerbrugge et al.* who investigated the effect of supplementation with 1 gram magnesium oxide for 6 weeks on Lp(a) level in hypercholesterolemic patients and did not observe a significant difference in serum magnesium increment.[46] *Held et al.* also, in a study which dealt with magnesium supplementation in 12 healthy persons, could not recognize a significant difference between two groups, despite detection of serum magnesium tendency toward increase in the supplementation group.[31] The study of *Rodriguez et al.*, which dealt with magnesium supplementation in the treatment of depression in diabetic elderly subjects, reported a significant difference in serum magnesium level in supplement group compared to placebo group.[47] *Haddad et al.* also, in their study, reported a significant increase in serum magnesium of the group which received intravenous magnesium compared to placebo group.[48] Guerrero and Rodriguez in their study to investigate the effect of magnesium supplement in lowering blood pressure of hypertensive diabetic patients, reported that during 4 month of supplementation with 450 mg/day elemental magnesium, serum magnesium concentration in the intervention group compared to placebo group, increased gradually and reached a significant level at the third month.[49] Regarding to this study and increment trend of serum magnesium in our study, this is possible that the duration of our study was inadequate to observe a significant difference in serum magnesium alterations. This resistance to change of serum magnesium levels could also be attributed to its important role as a cofactor and the need to precisely regulate its concentration.

The results of this study show that as compared to the placebo group, in the experimental group dietary magnesium supplementation brought about statistically significant increase in serum renin concentration ($P < 0.001$). There is little information about sleep deficiency and HPA axis in scientific literature.[50] Simultaneous measurement of plasma renin level and changes in different sleep phases suggests a close relationship between renin, and REM and NREM sleep. NREM sleep occurred in association with increased plasma renin level, but decreased renin level is concurrent with lighter sleep. Spontaneous or stimulated awakening results in stopping the normal increase of the plasma renin. Therefore, plotting renin levels will show exactly the sleep phases. If the sleep cycles are normal, renin level fluctuates in regular periods, but in incomplete sleep cycles, the renin plot will reveal all structural sleep disorders.[51] The results of our study are consistent with the results obtained from the study of *Held et al.* in which magnesium supplementation caused a significant increase in serum renin concentration in intervention group compared to placebo group. The proposed mechanism for this serum renin increment included sleep cycle alterations, and the endocrine glands which can affect the renin-angiotensin-aldosterone system activity through altering electrolytes level, including magnesium.[50] Some alterations occur in special regulatory pathways such as reduction of sensitivity to angiotensin II, due to sleep deficiency. Increased sleeping time, down-regulates inhibitory mechanism of renin release in kidney thus serum renin level increases. In adrenal cortex, it decrease aldosterone release and in hypothalamus, angiotensin II inhibits HPA axis.[52]

The results of our study show that magnesium supplementation resulted in significant decrease in serum cortisol concentrations. The results of the present study are consistent with the results of Held study which showed that Mg^{2+} supplementation caused significant cortisol reduction in the first half of the sleep.[31] However, *Cinar et al.* reported that magnesium supplementation of 10 mg per kilogram of the body weight, for one month, if associated with physical activity could cause the increase in serum cortisol level in individuals.[53] One possible mechanism for this reducing effect is that the NMDA antagonist properties of magnesium, reduce the activity and secretion of adrenocorticotropin from anterior hypophysis through down-regulation of corticotropin

releasing factor and its transportation via the main capillary network of hypophyseal port to anterior hypophysis. Which in turn, causes adenylyl cyclase activity in cell membrane of adrenal cortex, then reducing the activity of protein

kinase A and decreasing conversion of cholesterol to pregnenolone; the first and limiting reaction of cortisol synthesis. All mentioned actions are consistent with Mg^{2+} antagonistic properties on NMDA. Beside NMDA antagonistic properties, Mg^{2+} also has endocrine effects such as an ATII-antagonistic action[54] and a dampening effect on HPA-system activity[30] which results in decrease in serum cortisol concentration. The results of our study was not consistent with *Murck* and *Steiger* study, which in their study magnesium supplementation did not resulted in any decrement in serum cortisol concentrations. The solution they used in the treatment condition contained Mg^{2+} as well as glucose. So the question arises, whether the effects could be due to this agent. Regarding the endocrine changes, ACTH is known to be increased by hypoglycemia. The secretion of the releasing peptide for ACTH, corticotropin-releasing hormone, in isolated rat hypothalamus is stimulated by glucose levels under 5.5 mM. Above this level, the changes are small and not significant. Thus, it seems unlikely that glucose might contribute to the observed effects but this cannot be completely ruled out.

The results of our study showed that as compared to the placebo group, in the experimental group dietary magnesium supplementation brought about statistically significant increase in serum melatonin concentration ($P = 0.007$). Our result is consistent with the study of *Zhao et al*. which suggested that magnesium sulfate injection to experimental rats caused the stimulation and significant increase of melatonin secretion from pineal gland.[51] Also the results of this study are consistent with the results of *Billyard's* study which stated that magnesium deficiency led to plasma melatonin reduction in rats. The induced magnesium deficiency was medium in this study which then increases its capability to extend the results to human (because severe magnesium deficiency is rare in human). However, since only plasma melatonin was measured in this study, it is not clear that the melatonin reduction was due to reduced synthesis or increased destruction of melatonin.[55] On the other hand, the results of *Murck* and *Steiger* study showed that no change was observed in cortisol, growth hormone, prolactin, and melatonin secretions due to magnesium supplementation.[30]

In general, studies show that magnesium deficiency affects circadian cycle, melatonin reduction, and sleep disorders.[56,57] Morton and James suggested that the *N*-acetyltransferase (NAT) activity in rat is increased after magnesium injection. Moreover, magnesium increases NAT activity in pineal gland *in vitro*, suggesting that the pineal gland, not another place of the body, is the affect site.[58] The mentioned findings implicates on possible magnesium deficiency role in reduced NAT activity and reduced melatonin production.

CONCLUSION

Supplementation of magnesium appears to improve subjective and objective measures of insomnia in elderly people and may become a useful instrument in managing sleep disorders in the elderly, which could also be extended as a helpful aid to the general population.

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