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Serum Magnesium Status in Patients Subjects with Depression in the City of Yazd in Iran 2013–2014

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Abstract Depression is the most common mental disorder and involves many factors. The regulatory effects of magnesium on N-methyl-D-aspartate (NMDA) channels make it a factor in the treatment of depression. The present study investigated the level of serum magnesium in subjects diagnosed with depression in the city of Yazd in Iran. This cross-sectional study was done from January 2013 to January 2014 on 650 patients with depression who agreed to participate in this study. Diagnosis was made using the Beck Depression Inventory test (BDI-II); those scoring higher than 11 were sent to the medical school laboratory for further testing of serum magnesium levels. The mean age of the patients was 34.16±9.12 years. Of the 650 subjects, 195 were male (30 %) and 455 were female (70 %). The total mean serum magnesium was 2.1±0.26 mg/dl. The prevalence of hypomagnesemia 13.7 %, hypermagnesemia 8.3 %, and sub-optimal magnesium levels was 26.5 %. Sub-optimal prevalence in women (28.1 %) was higher than in men (26.2 %). A significant relationship was observed between depression and serum magnesium level (p=0.02). The results indicated that the prevalence of hypomagnesemia in subjects diagnosed with depression is high compared to non-depressed individuals. Moreover, there was a significant relationship between hypomagnesemia and intensity of depression that suggests a role for this element in the pathogenesis of the disorder. The high sub-optimal prevalence among women indicates that increased attention should be paid to this group.

Keywords Depression · Magnesium · NMDA · Hypomagnesemia

Introduction

Mental disorders are prevalent worldwide and constitute about 36 % of all non-communicable diseases [1, 2]. An estimated 400 million people suffer from depression globally, making it a primary mental disorder. Depression is more prevalent in women than in men [3, 4]. About 20 % of women and 10 % of men are affected by depression globally [5]. The World Health Organization reports that depression will become the second leading cause of disease burden worldwide by 2020 [6]. The prevalence of depression differs by country. It has been estimated to be 4.1 % in Iran, which is a moderate figure compared to other countries [7].

The cognitive symptoms of depression include changes in mental focus, difficulty in decision-making, feelings of guilt and worthlessness, and physical symptoms such as changes in appetite and sleep habits that can significantly reduce the quality of life [8, 9]. It is estimated that 3.8 % of disability-adjusted life years are related to depression and the disorder can impose heavy costs on the patient [9, 10]. Depression is blamed for a 40 to 60 % increase in the rate of premature death and suicide [11]. Depressed persons are at high risk of chronic diseases such as diabetes, high blood pressure, and cancer [4, 12]. Recent studies have shown that depression is an independent risk factor for cardiovascular disease [13].

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Although the main cause of depression is not well-known [14], several studies suggest that a number of factors contribute to its incidence. Investigations have shown that the contribution of genetics to the incidence of depression is 27 % [15]. Other important contributing factors are hormonal, immunological, biochemical, and dietary [16]. The role of micronutrients as coenzymes, especially bivalent minerals such as magnesium, is controversial in the study of disease [17, 18]. Magnesium is the second most common intracellular bivalent cation and has an important physiological role in many metabolic pathways [19]. This element contributes to the functioning of more than 300 types of enzymes, hormones, and neurotransmitters [19, 20] and to the synthesis of fatty acids, protein, carbohydrates, and to memory, learning, and the sustainable structure of the ATP [19, 21, 22]. Recent studies have shown that magnesium serves a protective role for neurons [23, 24]. The effect of the magnesium deficiency on the central nervous system is complex and poorly understood [25] [26].

One possible reason for the relation between magnesium and depression is its inhibitory effect on the N-methyl-D aspartate (NMDA) channels in the brain [26]. These channels are found in high concentrations in the cortical and limbic system and affect the cognitive, conceptual, and psychological functioning of individuals [27]. Several studies have focused on the role of these channels in anxiety and depression [26, 28]. Although magnesium has been suggested as an effective element on NMDA channels in several studies, the correlation between serum magnesium levels and depression remains controversial [26, 29].

The prevalence of hypomagnesemia in the general population of Iran has been reported to be 4.6 % [30], but its correlation with depression has been rarely studied. There is a wide variety of effects, particularly neurological, of magnesium on the human body and also a high incidence of depression. The present study evaluated the level of serum magnesium in subjects diagnosed with depression in the city of Yazd.

Materials and Methods

Study Design and Subjects

This cross-sectional study was conducted from January 2013 to January 2014. Initially, a public announcement about the study in Yazd invited interested individuals to participate in the study for further assessment of depression. The Beck Depression Inventory test (BDI-II) was administered to participants to assess their diagnosis of depression. Those who were selected for the study totaled 650 patients who scored higher than 11 on the BDI-II; these were sent to a laboratory for assessment of their serum magnesium levels. The criteria for selection of subjects were as follows: being 20 to 60 years of age; having no history of malignancy, high blood pressure, diabetes, cardiovascular disease, or cancer; and not having consumed multivitamin mineral supplements, diuretics or cardiac glycosides within the previous 3 months. To assess the prevalence of hypomagnesemia (6.4 %) at 0.05 α and 0.7 % accuracy, it was estimated that 600 samples were required. To increase the accuracy of the results, this figure was increased to 650.

Measurements

BDI-II was used to assess depression levels. This is a new version of the self-report questionnaire and contains 21 questions that measure symptoms of depression such as sleep disturbance, lack of appetite, self-confidence, hope, and a sense of sadness to assess the severity of depression in adolescents and adults. This version is applied for evaluation of symptoms based on diagnostic criteria for depression from the American Psychiatric Association in the DSM-fourth edition, and it was validated in Persian language [31, 32].

Each multiple choice question has four options scored from 0 to 3 according to the severity of depression. The total score was calculated for each individual using the values provided for each question. Possible scores range from 0 to 63. These total scores are used to classify respondents into six groups: 0–10 (not depressed), 11–16 (mild depression), 17–20 (in need of counseling), 21–30 (depression), and 31–40 (severe depression). Scores greater than 40 were defined as very severe depression. Individuals who scored above 11 and met the inclusion criteria were selected for the study. These were interviewed and completed a generic information questionnaire. They were then sent to the central laboratory of Shahid Sadoughi University of Medical Sciences in Yazd to determine their serum magnesium levels.

The laboratory collected 5-ml fasting blood samples from each individual in the evening. To determine serum magnesium levels, the photometric method was administered using a magnesium xylidyl blue assay kit (Pars Azmun; Iran) with a sensitivity rate of 0.2 mg/dl. The normal range for men was 1.8–2.6 mg/dl and for women was 1.9–2.5 mg/dl. Individuals with serum magnesium levels above normal range are known as hypermagnesemic, and those with lower magnesium serum levels above normal range are considered hypomagnesemic. Serum magnesium levels below 1.80 mg/dl are considered to be sub-optimal for both females and males [30].

Data Analysis

SPSS 16 software was used for analysis of data. The Kolmogorov-Smirnov test was used to assess data distribution. The Student *t* test and one-way ANOVA were used to compare means. For comparison of frequency distributions of

Table 1 The mean of serum magnesium in terms of different studied variables

Characteristics	*N* (%)	mean±SD	95 % confidence interval	*p* value
Gender				
Male	195 (30)	2.13±0.28	2.09–2.17	0.49[a]
Female	455 (70)	2.08±0.26	2.06–2.11	
Marital Status				
Single	101 (15.5)	2.07±0.23	2.02–2.12	0.37[b]
Married	534 (82.2)	2.10±0.27	2.08–2.12	
Divorced	12 (1.8)	2.21±0.27	2.03–2.38	
Widow	3 (0.5)	2.09±0.41	1.06–3.12	
Education				
Illiterate	11 (1.7)	1.94±0.22	1.79–2.10	0.39[b]
Elementary	151 (23.2)	2.09±0.24	2.05–2.13	
Diploma	239 (36.8)	2.12±0.29	2.08–2.15	
Associate Degree	52 (8.0)	2.10±0.26	2.03–2.17	
B.S.	158 (34.3)	2.09±0.25	2.05–2.13	
Above	34 (5.2)	2.11±0.23	2.05–2.13	
Occupation				
Unemployed	74 (11.4)	2.06±0.23	2.07–2.11	0.13[b]
Self-employment	124 (19.1)	2.41±0.26	2.10–2.20	
Employee	125 (19.2)	2.09±0.28	2.04–2.14	
Housewife	310 (47.7)	2.09±0.26	2.06–2.12	
Retired	16 (2.5)	2.07±0.29	1.92–2.23	
Age (year)				
20–29	262 (40.3)	2.07±0.26	2.04–2.10	0.06[b]
30–39	244 (37.5)	2.13±0.26	2.10–2.17	
40–49	103 (15.8)	2.09±0.27	2.04–2.15	
≤50	41 (6.3)	2.06±0.25	1.98–2.14	
Depression status				
Slight	40 (6.2)	2.04±0.22	1.97–2.11	
Need Advice	108 (16.6)	2.10±0.28	2.05–2.15	0.58[b]
Relatively depressed	252 (38.8)	2.09±0.24	2.06–2.13	
Severe	184 (28.3)	2.12±0.27	2.08–2.16	
Very severe	66 (10.2)	2.08±0.32	2.00–2.16	
Months				
March	20 (3.1)	2.03±0.21	1.93–2.13	0.01[b]
April	87 (13.4)	2.11±0.27	2.05–2.16	
May	118 (18.2)	2.14±0.24	2.10–2.19	
June	17 (2.6)	2.18±0.22	2.06–2.29	
July	112 (17.2)	2.11±0.27	2.06–2.17	
August	34 (5.2)	2.07±0.28	1.97–2.16	
September	48 (7.4)	2.07±0.27	1.99–2.15	
October	15 (2.3)	2.03±0.47	1.77–2.30	
November	29 (4.5)	2.13±0.32	2.01–2.26	
December	76 (11.7)	2.22±0.26	2.12–2.33	
January	69 (10.6)	2.05±0.21	2.0–2.1	
February	25 () 3.8	2.02±0.23	1.97–2.08	
Seasons				0.17[b]
Spring	225 (34.6)	2.12±0.25	2.09–2.15	
Summer	163 (25.1)	2.11±0.27	2.07–2.15	
Autumn	92 (14.2)	2.09±0.32	2.02–2.15	
Winter	170 (26.2)	2.06±0.23	2.03–2.10	

[a] Student's *t* test

[b] One way ANOVA

Table 2 Frequency distribution of serum magnesium status in terms of studied variables

Variables	Hypomagnesemia *N* (%)	Normal *N* (%)	Hypermagnesemia *N* (%)	*p* value[a]
Women				
Age (year)				
20–29	23 (4.12)	159 (85.9)	3 (1.6)	0.7
30–39	22 (12.7)	148 (85.5)	3 (1.7)	
40–49	12 (17.1)	57 (81.4)	1 (1.4)	
≤50	1 (3.7)	26 (96.3)	0 (0)	
Men				
Age (year)				
20–29	14 (18.4)	58 (76.3)	4 (5.3)	0.04
30–39	7 (9.9)	56 (78.9)	8 (11.3)	
40–49	4 (12.1)	24 (72.7)	5 (15.2)	
≤50	6 (42.9)	7 (50)	1 (7.1)	
Gender				
Female	58 (12.7)	390 (85.7)	7 (1.5)	0.001
Male	31 (16)	145 (74.7)	18 (9.3)	
Marital Status				
Single	15 (15)	82 (82)	3 (3)	0.70
Married	73 (13.7)	440 (82.4)	21 (3.9)	
Divorced	1 (6.7)	13 (86.6)	1 (6.7)	
Education				
Illiterate	2 (18.2)	9 (81.8)	0 (0)	0.70
Elementary	18 (11.9)	130 (86.1)	3 (2.0)	
Diploma	32 (13.4)	193 (80.8)	14 (5.9)	
Associate Degree	6 (11.8)	43 (84.3)	2 (3.9)	
B. S.	26 (16.5)	127 (80.4)	5 (3.2)	
Above	3 (8.8)	30 (88.2)	1 (2.9)	
Occupation				
Unemployed	13 (17.8)	60 (82.2)	0 (0)	0.04
Self-employment	15 (12.1)	99 (79.8)	10 (8.1)	
Employee	18 (14.4)	99 (79.2)	8 (6.4)	
Housewife	40 (12.9)	264 (85.2)	6 (1.9)	
Retired	3 (18.8)	12 (75)	1 (6.2)	
Month				
March	3 (15)	16 (80)	1 (5)	0.68
April	10 (11.6)	71 (82.6)	5 (5.8)	
May	9 (7.6)	104 (88.1)	5 (4.2)	
June	1 (5.9)	16 (94.1)	0 (0)	
July	17 (15.2)	88 (78.6)	7 (6.2)	
August	8 (23.5)	24 (70.6)	2 (5.9)	
September	8 (16.7)	39 (81.2)	1 (2.1)	
October	3 (20)	12 (80)	0 (0)	
November	3 (10.3)	25 (86.2)	1 (3.4)	
December	13 (17.1)	62 (81.6)	1 (1.3)	
January	12 (17.4)	56 (81.2)	1 (1.4)	
February	2 (8)	22 (88)	1 (4)	
Season				
Spring	22 (9.8)	191 (85.3)	11 (4.9)	0.18
Summer	26 (16)	128 (78.5)	9 (5.5)	
Autumn	14 (15.2)	76 (82.6)	2 (2.2)	

Table 2 (continued)

Variables	Hypomagnesemia *N* (%)	Normal *N* (%)	Hypermagnesemia *N* (%)	*p* value[a]
Winter	15 (15.9)	140 (82.4)	3 (1.8)	
Age (year)				
20–29	37 (14.2)	217 (83.1)	7 (2.7)	0.68
30–39	29 (11.9)	204 (83.6)	11 (4.5)	
40–49	16 (15.5)	81 (78.6)	6 (5.8)	
≤50	7 (17.1)	33 (80.5)	1 (2.4)	
Depression status				
Mild	10 (25)	30 (75)	0 (0)	0.02
Need advice	20 (18.5)	82 (75.9)	6 (5.6)	
Relatively depressed	24 (9.5)	222 (88.1)	6 (2.4)	
Severe	22 (12)	151 (82.5)	10 (5.5)	
Very severe	13 (19.7)	50 (75.8)	3 (4.5)	
Total	89 (13.7)	536 (82.5)	25 (3.8)	

[a] Chi-square test

qualitative variables, the chi-square test was used. A p value of less than 0.05 was considered significant.

Results

Of the 650 participants, 195 (30 %) were male and 455 (70 %) were female. The overall mean age was 34.16±9.12 years; for females, this value was 34.04±0.42, and for males it was 34.44±0.67. Table 1 shows the distribution of the variables and mean serum magnesium levels. As shown, most participants were married (82.2 %) and nearly half (47.5 %) had university education.

The BDI-II classification of depression showed that 38.5 % of participants were suffering from severe or very severe depression. The sampling continued for one year. It was noted that the number of samples increased in May, in the spring, in January and in winter. The mean serum magnesium in the subjects was 2.1±0.26 mg/dl. There was a significant difference in mean serum magnesium between months; this was not observed for any other variables.

Table 2 shows the distribution of serum magnesium versus the variables studied. Of the total study population, 89 subjects (13.7 %) were hypomagnesemic, 25 (3.8 %) were hypermagnesemic, and 536 patients (82.5 %) had normal values. There were significant differences only between serum magnesium levels and gender, employment, and depression. As shown, 85.7 % of women had normal serum magnesium levels compared to 74.7 % of men. The prevalence of abnormal serum magnesium was greater for men than for women.

The frequency distribution of magnesium by age was significant only for men. The number of subjects with hypomagnesemia who were diagnosed with severe depression was greater than for subjects diagnosed as mildly depressed or in need of counseling. A total of 33.4 % of subjects who were severely and very severely depressed recorded deficiencies in serum magnesium. The total for subjects diagnosed with mild depression or in need of counseling was 28 %. The overall percentage of 26.5 % sub-optimal magnesium incidence broke down to 28.1 % for women and 22.6 % for men.

Discussion

The serum magnesium levels of depressed subjects in Yazd indicated a prevalence of hypomagnesemia in the overall population (13.7 %). This rate was significantly higher in men than in women. The prevalence of hypomagnesemia in the general population has been reported in various studies [30, 33–35]. Syedmoradi et al. reported a <1.82 mg/dl prevalence in 804 normal individuals aged over 20 years; of the 4.6 % of residents with hypomagnesemia in Tehran, the rate was 6 % for women and 3.2 % for men [30]. The percentage in the present study in Yazd was almost double that of the non-patient population of Tehran.

A study of 3421 individuals in Spain reported a hypomagnesemia rate of <1.70 mg/dl for the 25–60 year age group and revealed a rate of 8.82 % for women, which was significantly higher than the rate for men [35]. Cheungpasitporn et al. conducted a cohort study of 65,974 patients admitted to Minnesota hospitals with cutoff points similar to those from the present study. They reported a hypomagnesaemia prevalence of 31.5 %, with a higher prevalence among patients with hematologic and oncological disorders [36]. Gongora studied 2447 individuals in Mexico aged 12–19 years and found the prevalence of hypomagnesemia (<1.82 mg/dl) to be 37.6 %, although this amount did not significantly correlate with age or other factors [34]. Sales et al. carried out a survey of plasma magnesium levels in 115 Brazilian students and reported 34 % prevalence of hypomagnesemia and found no significant difference between genders [37]. As seen in Table 2, only for men did the hypomagnesemia rate significantly correlate with age. The percentage tended to increase as age increased and most studies reported a higher incidence for women than for men [30, 35]. The reason for this difference is unknown.

The balance of magnesium in the body depends on the intake of adequate amounts and sufficient absorption from the intestine without excessive excretion in the urine [20]. Inadequate intake of magnesium can stem from inadequate intake of vegetables and is an important factor for the difference in serum magnesium in different regions [38, 39]. Cereal is a magnesium-rich food source, but it loses 82 to 97 % of its magnesium content during processing [40]. Studies have shown an association between an increased risk of depression and low fruit and vegetable intake, a diet high in processed foods, including excessive consumption of refined carbohydrates, fried and processed foods such as pizzas and hamburgers which contain no magnesium and are rich in glutamates [41, 42].

Depression may also be adversely affected by the functioning of the gastrointestinal tract. A study carried out on 23,698 patients who underwent endoscopies, showed that depression is a major risk factor for irritable bowel syndrome, indigestion, reflux, peptic ulcers, and stomach and colorectal cancer. These conditions increase the risk of nutritional deficiencies by adversely affecting digestion and absorption of nutrients [43]. In addition to the differences in dietary patterns in different regions, genetics may play a role in serum magnesium levels of about 27 % [30].

In the present study, a 26.5 % incidence of sub-optimal serum magnesium was observed and the rate among women was higher than among men. Syedmoradi reported a cutoff point of 14.6 % [30]. The importance of checking the level of sub-optimal serum magnesium is clear when latent magnesium deficiency (subclinical magnesium deficiency) is considered. A slight deficiency in serum magnesium caused by inadequate amount intake, insufficient absorption of magnesium from the intestine, and/or excretion in the urine causes decreased magnesium content leading to a decrease in mineral content in bones. In this context, the magnesium content may be normal, but in the long run the inadequacy decreases the bone content and eventually decreased serum magnesium serum to below normal range [37, 44, 45].

The present study showed that the overall prevalence of hypermagnesemia was 3.8 %, which is similar to a study in Tehran among non-depressed people (3 %) [30]. The prevalence of hypermagnesemia was reported to be 20.2 % by Cheungpasitporn et al., with a higher prevalence among patients with cardiovascular disease [36]. The importance of hypermagnesemia relates to the interaction of magnesium and parathyroid hormone. Numerous studies have shown that an increase in serum magnesium suppresses parathyroid activity; this in turn will affect vitamin D and calcium metabolism in the body [46]. Meta-analysis revealed a positive significant relationship between depression and hypomagnesemia. The relative risk associated with depression has been estimated to be 1.34 among patients with hypermagnesemia [47], which may relate to the link between magnesium and NMDA receptors. NMDA receptors are glutamate-dependent ionotropic canals that are activated when glutamate is released from a presynaptic terminal, leading to an influx of Na+and Ca+into the neurons. Because calcium is a cofactor for enzyme activity, it can activate different enzymes in different pathways. Calcium activates enzymes, catalyzing the production of nitric oxide (NO) by increasing this neurotransmitter, which then stimulates delivery of glutamate to presynaptic neurons [17, 48]. It also activates protein kinase complex, which increases the number of NMDA receptors on the surface and consequently improves the influx of calcium into cells. The presence of magnesium, however, inhibits the function of NMDA channels and the influx of calcium into cells, preventing stimulation of an enzyme cascade [49].

An important strength of the present study was evaluation of levels in subjects over the course of 1 year, which has not previously attempted. A limitation of this study is the lack of a non-depressed control group. The role of magnesium supplementation for depressed individuals who are suffering from magnesium deficiency is a future step toward clarifying the role of magnesium in depression. A study of the effects of magnesium supplementation is recommended.

Conclusions

The results indicate a prevalence of hypomagnesemia in patients with depression compared to non-depressed subjects. Hypomagnesemia and depression may be associated and the role of this element in the pathogenesis of this disease may be indicated. It is necessary to encourage proper nutrition for prevention and treatment of depression. Because there is a higher incidence of sub-optimal serum magnesium in women, this segment of the population requires more attention.

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