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Evaluation of Serum Magnesium Levels in Patients with the Diagnosis of Depressive Disorder Applied to a Psychiatry Clinic: A Retrospective Study

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ABSTRACT
Objective: The role of magnesium in the pathophysiology of depression has increased the interest in magnesium. Therefore, in this study, we aimed to evaluate serum magnesium levels in patients diagnosed with depressive disorder who applied to the psychiatry outpatient clinic. **Materials and Methods:** The data of 1013 patients who were diagnosed with depressive disorder and whose serum magnesium levels were measured were included in the study by retrospectively scanning the data of the patients who had applied to the Psychiatry outpatient clinic of Balıkesir University Faculty of Medicine between July 2020 and July 2022. Since the serum glucose, GGT and creatinine values were above their reference ranges in 183 of 1013 patients included in the study, the data of these patients were excluded from the analysis. **Results:** Serum magnesium values of 12.9% of female and 9.1% of male patients were below the reference values (1.9-2.7 mg/dl). The mean (±SD) magnesium values of all patients, female and male patient groups were statistically significantly different from the population mean. (2.02±0.15 mg/dl, 2.01±0.16 mg/dl and 2.04±0.15 mg/dl ; P<0.001, P<0.001, and P<0.001, respectively). No statistically significant relationship was observed between magnesium levels and age of the patients. **Conclusion:** In our study, hypomagnesemia was observed in 11.9% of patients with a diagnosis of depressive disorder. For this reason, we thought that if hypomagnesemia is detected in patients followed up with depressive disorder, its replacement may be important as it may be effective in reducing depressive symptoms.
Keywords: Magnesium, Depression, Adjunctive therapy, Antidepressants.

Bir Psikiyatri Kliniğine Başvuran Depresif Bozukluk Tanısıyla Başvuran Hastalarda Serum Magnezyum Düzeylerinin Değerlendirilmesi: Retrospektif Bir Çalışma

ÖZ
Amaç: Magnezyumun depresyon patofizyolojisindeki rolü, magnezyuma olan ilgiyi artırmıştır. Ancak literatürde depresyonda magnezyum düzeylerinin azalıp azalmadığına ilişkin çelişkili sonuçlar bildirilmektedir. Bu nedenle bu çalışmada psikiyatri polikliniğine başvuran depresif bozukluk tanılı hastalarda serum magnezyum düzeylerinin değerlendirmesi amaçlanmıştır. **Gereç ve Yöntem:** Temmuz 2020-Temmuz 2022 tarihleri arasında Balıkesir Üniversitesi Tıp Fakültesi Psikiyatri polikliniğine başvuran hastaların verileri retrospektif olarak taranarak depresif bozukluk tanısı konulan ve serum magnezyum düzeyleri ölçülen 1013 hastanın verisi geriye dönük taranarak çalışmaya dahil edildi. Çalışmaya alınan 1013 hastanın 183'ünde serum glukoz, GGT ve kreatinin değerleri referans değerlerinin üzerinde olduğu için analiz dışı bırakıldı. **Bulgular:** Kadın hastaların %12.9'unun, erkek hastaların %9,1'inin serum magnezyum değerleri referans değerlerin (1,9-2,7 mg/dl) altındaydı. Tüm hasta, kadın ve erkek hasta grubu ortalama (±SD) magnezyum değerleri, toplum ortalamasına göre istatistiksel olarak anlamlı derecede farklıydı (2.02±0.15 mg/dl, 2.01±0.16 mg/dl ve 2.04±0.15 mg/dl ve P<0.001, P<0.001 ve sırasıyla P<0.001). Kadın ve erkek hastaların ortalama (±SS) yaşları sırasıyla 43.77(±15.43) ve 43.05 (±17.75) olarak bulundu. Magnezyum düzeyleri ile hastaların yaşı arasında istatistiksel olarak anlamlı bir ilişki gözlenmedi. **Sonuç:** Çalışmamızda depresif bozukluk tanılı hastaların %11.9'unda hipomagnezemi görülmüştür. Bu nedenle depresif bozukluk ile izlenen hastalarda hipomagnezemi saptanırsa depresif belirtilerin azaltılmasında etkili olabileceğinden replasmanının önemli olabileceğini düşünülmüştür.
Anahtar Kelimeler: Magnezyum, Depresyon, Adjuvan Terapi, Antidepresanlar.

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INTRODUCTION

Depressive disorders are very common and costly disorders that are associated with reduced functioning and quality of life, medical comorbidity, and mortality. The global prevalence of depressive disorders has been reported to reach 268.2 million people worldwide (Vos et al., 2017). The neurobiological basis of depression is dysfunction in monoaminergic neurotransmission, particularly serotonergic dysregulation. Since the 1950s, the monoamine theory and selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have influenced the development of antidepressant treatments (Morrissette & Stahl, 2014). The limitations of explaining and treating depression with the monoamine hypothesis, and the findings of a rapid antidepressant response to ketamine in patients with resistance to antidepressant therapy have shed light on the development of new antidepressant compounds and adjunctive therapy strategies (Berman et al., 2000).

Many different types of antidepressant drugs are currently available in the research and development of depression treatments and have been shown to be effective in randomized trials (Cipriani et al., 2018). Despite this fact, patients may find it difficult to find safe, tolerable, fast, effective and inexpensive treatment. At the same time, treatments such as antidepressant medications and psychotherapies can take weeks to take effect and often fail to completely relieve symptom. (Jorm, Patten, Brugha & Mojtabai, 2017).

Depressive disorders are currently one of the largest health expenditure categories, due to patients who are resistant to current treatments. Therefore, alternative treatment strategies gain importance. Among the alternative treatment strategies, ketamine is a possibly fast-acting compound used mainly in treatment-resistant cases. Initially used as an anesthetic and sedative agent, this drug has an antidepressant effect that occurs within hours and lasts for several days (Andrade et al., 2017).

Presumably, the functional results of ketamine and magnesium treatment show similarities. After administration of magnesium to mice, similar to the effects of ketamine, BDNF (Human Brain-Derived Neurotrophic Factor) expression increased in the brain of mice and synaptic sprouting occurred in their prefrontal cortex (Abumaria et al., 2011). Both ketamine and magnesium cause similar changes, such as increased expression of eukaryotic elongation factor- 2 and BDNF and exert similar effects on slow-wave sleep in humans (Duncan et al., 2012). Magnesium is the fourth most abundant mineral in the human body (Jorm, Patten, Brugha & Mojtabai, 2017), and it regulates various biochemical reactions in the body, including protein synthesis, muscular force, nervous impulse, and neuromuscular transmission, signal transduction, blood sugar and blood pressure, and vitamin D production. It is a cofactor in more than 1,000 enzyme systems and is required for the structural function of proteins, nucleic acids or mitochondria (Gröber, Schmidt & Kisters, 2015).

Magnesium is also an endogenous N-methyl D-aspartate receptor (NMDAR) antagonist (Castiglioni, Cazzaniga, Albisetti & Maier, 2013) and has anti-inflammatory properties that are closely related to depression, so magnesium deficiency in the brain can lead to excitotoxicity and the production of Reactive Oxygen Species (ROS) (Kim, Na & Myint, 2016).

Magnesium controls the HPA (hypothalamus-pituitary-adrenal) axis by reducing the release of adrenocorticotropic hormone (ACTH) and regulating ACTH sensitivity. Thus, magnesium can prevent the hyperactivation of the HPA axis seen in patients with depressive disorder (Wang, Um, Dickerman & Liu, 2018). Again, the effect of magnesium on the glutamatergic system has been compared to that of the glutamatergic regulator ketamine, which has fast-acting antidepressant effects (Górska et al., 2019). The ketamine-like effects of magnesium and the antidepressant properties of ketamine have increased attention to magnesium. At the same time, the relationship between magnesium and psychiatric diseases has attracted the attention of researchers, since magnesium has important functions in the central nervous system and can be easily measured in the blood.

Many studies have observed a relationship between depression and magnesium levels, but there are confusing results about the underlying functional mechanism of this relationship (Cubała, Landowski, Szyszko & Czarnowski, 2014).

Therefore, in our study, we aimed to evaluate serum magnesium levels in patients diagnosed with depressive disorder who applied to the psychiatry outpatient clinic. Our hypothesis is that patients followed up with depressive disorder have lower serum magnesium levels than the population average. Thus, we aimed to better understand the role of serum magnesium levels in the possible pathophysiology of depression and to present it as a treatment option in depression.

MATERIALS AND METHODS

In this research study, the data of patients with a diagnosis of depressive disorder (ICD-10; F32- F32,9) were scanned, and the data of 1013 patients whose serum magnesium levels were checked retrospectively through the hospital information management system were included in the study.

The first measured magnesium levels at the admissions of the patients were taken into account and among this patient group, the data of the patients whose serum creatinine, GGT and glucose levels were outside the reference range due to systemic diseases that could affect the serum magnesium levels, and those with a history of malabsorptive diseases (eg, Crohn's disease,

ulcerative colitis, celiac disease, etc.) were excluded from the study.

Statistical analysis

The data were recorded in the Microsoft Excel 2016 program and SPSS 25.0 package program through the hospital information management system, and statistical analyzes were carried out through these programs. The distribution of the data was evaluated using appropriate statistical methods (Kolmogorov-Smirnov or Shapiro-Wilk tests) and visual graphics (histogram etc.). Student's t test or Mann- Whitney U test was used in the comparison of both groups, taking into account the distribution of the data. The chi-square test was used in the analysis of categorical data. In order to determine the relationship between the data, the Pearson correlation test was used for normally distributed data, and the Spearman correlation test was used for the evaluation of data that did not show normal distribution. $P<0.05$ was accepted as the level of statistical significance**.**

Ethical considerations

Before starting the study, ethical approval (decision no. 2022/81) was obtained from Balikesir University Health Sciences Non-Interventional Research Ethics Committee on 08.16. 2022.

RESULTS

Within the scope of this study, serum magnesium levels of the patients diagnosed with depressive disorder who applied to the psychiatry clinic were examined. Thus, the possible relationship between serum magnesium levels and age, gender and population mean magnesium levels was evaluated.

Systemic diseases (diabetes mellitus, alcoholism, acute-chronic, renal failure) that could potentially affect serum magnesium levels were scanned in a total of 1013 patients included in the study, and 183 patients whose serum glucose, GGT and creatinine values were above the reference ranges were excluded from the study. (Figure 1).

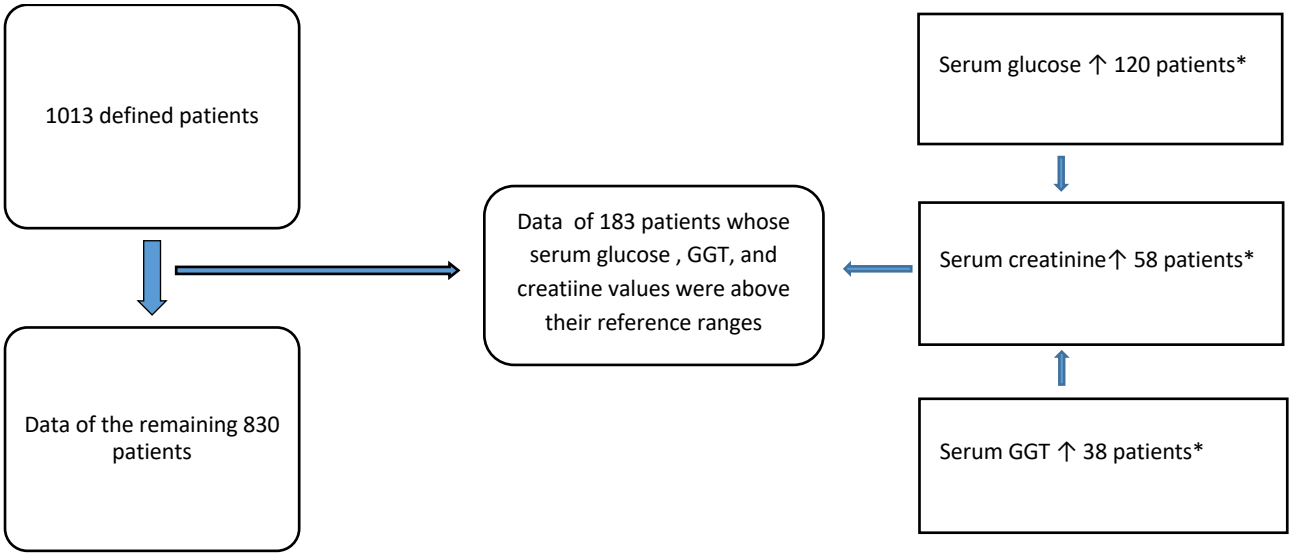

Figure 1. Patient group.

*Among 1013 patients included in the study, both serum glucose and creatinine values of 11; both serum glucose values and GGT values of 11 and both serum creatinine and GGT values of 3 patients were above the reference ranges. The remaining 830 patients consisted of 611 (73.6%) female, and 219 (26.3%) male cases. The mean (±SD) ages of female (43.77±15.43), male (43.05±17.75), and the whole patient groups (43.58±16.07) were as indicated (Table 1).

Table 1. Descriptive statistics.

	Female (N=611)	Male (N=219)	Total (N=830)
Gender	73.6%	26.3%	100%
Age (Mean±SD) (years)	43.77±15.43	43.05±17.75	43.58±16.07
Mg+2(Mean±SD) (mg/dl)	2.01±0.16	2.04±0.15	2.02±0.15

Table 2. Magnesium average statistics.

Beckman Coulter;1.9-2.7 mg/dl(2.3 mg/dl)	>2.3 mg/dl	<2.3 mg/dl
Female	87.1%	12.9%
Male	90.9%	9.1%
Total	88.1%	11.9%

The population average value of magnesium was taken as 2.3 mg/dl according to the data of the manufacturer (Beckman Coulter; 1.9-2.7 mg/dl). The mean (±SD) value of magnesium in the total patient group was 2.02±0.15 mg/dl, with a statistically significant difference when compared with the population mean. (P<0.001).

The mean (±SD) values of magnesium in the female and male patient groups were 2.01±0.16 mg/dl and 2.04±0.15 mg/dl, respectively, with a statistically significant difference when compared with the population mean. (P<0.001, P<0.001). Serum magnesium values were below their reference ranges in 11.9% of all, 12.9% of female and 9.1% of male patient groups. (Table 2) Any statistically significant correlation could not be found between magnesium levels and age according to Pearson correlation analysis. (r=-0.19, P=0.589)

DISCUSSION

In this retrospective study, 830 adult patients with measured serum magnesium levels who applied to the psychiatry clinic and were followed up with a diagnosis of known depressive disorder were examined by considering factors such as age, gender and underlying systemic diseases.

To summarize our results, when magnesium values of the patients followed up for depressive disorder in our study were evaluated based on the population magnesium average data of the manufacturer of the laboratory device used in the study; we observed that the serum magnesium values of 11.9% of the total patient group, 12.9% of the female and 9.1% of the male patient groups were below the reference values. When the mean (±SD) magnesium values of the total patient, female and male patient groups were compared with the population mean, a statistically significant difference was found between them. Any statistically significant relationship was not observed between magnesium levels and age according to Pearson correlation analysis.

Nutrients, including vitamins, minerals, fatty acids, and essential amino acids, affect neurological hormonal, neurotransmitter, and signaling pathways that modulate brain function, including cognitive functions and mood (Lang et al., 2015).

In rodent studies, magnesium deficiency has been shown to cause depression-like behavior (Singewald et al., 2004). Similarly, it has been observed that the administration of magnesium in addition to antidepressants in rodents can augment the beneficial effects of antidepressants (Poleszak et al., 2007).

A randomized controlled trial by Tarleton et al. with 126 adult participants demonstrates the antidepressive properties of magnesium and its potential use as an additive to antidepressant therapy. Chronic magnesium supplementation appears to improve depressive disorder symptoms even without a prior diagnosis of magnesium deficiency (Tarleton et al., 2017). In studies and case reports cited in the literature, the relationship between low serum magnesium levels of the patients followed up with depressive disorder and the possible antidepressant effects of magnesium has been emphasized (George & Karen, 2006).

Contrarily, some studies have associated patients with depressive disorder with high magnesium levels (Misztak, Opoka & Topór-Mądry, 2015). In a study of 53 patients with depression followed up without medication, Widmer et al. had divided patients into three groups according to the severity of the depression and compared them with 48 healthy volunteers and found that patients with moderate and high levels of depression had higher erythrocyte magnesium and also plasma Mg levels than patients with low depression or controls (Widmer et al., 1995). In a former study, Widmer et al. had observed that patients with a diagnosis of depressive disorder followed up without medication had higher erythrocyte and plasma magnesium than controls (Widmer et al., 1992). In the light of this information, although magnesium measurement methods seem to affect the results of the studies, the important functions of magnesium and the fact that hypomagnesemia is associated with a hyperexcitable state raises the question of whether high magnesium levels may have been found as a response to the possible negative effects of hypomagnesemia in untreated depressive disorder patients.

Since most of the magnesium is found inside cells or in bone it is difficult to assess serum magnesium levels. The most common and valuable test in clinical medicine for the rapid assessment of changes in magnesium levels is to measure serum magnesium concentration. However, serum magnesium levels do not correlate sufficiently with total body magnesium levels, or concentrations in certain tissues (Ismail & Ismail, 2010).

Bone is the most important reservoir for magnesium (approximately 60% of total body magnesium). Magnesium deficiency affects bone directly by reducing bone stiffness, increasing osteoclasts and reducing osteoblasts and indirectly by interfering with PTH and vit D synthesis with resultant aggravation of inflammation/oxidative stress and subsequent bone loss. Studies have shown that compared to healthy controls, osteoporotic patients have lower serum magnesium levels (Mederle et al., 2018). However, in our study any statistically significant relationship was not observed between magnesium levels and age according to Pearson correlation analysis. Consistent with the literature data, in our study the female patient group was more closely associated with hypomagnesemia relative to the male patient group.

Depression is an important health problem in elderly patients and nutritional factors seem to predispose to the development of depression (Chrzastek, Guligowska, Sobczuk & Kostka, 2022). Considering that hypomagnesemia will increase the severity of depressive symptoms with the contribution of the osteoporotic process, it is important to develop optimal dietary recommendations and perform magnesium replacement, especially in the elderly female population with depressive symptoms.

In the light of studies, it is predicted that enhancing the therapeutic efficacy of antidepressant drugs with various supplements such as magnesium targeting nutritional and physiological factors can increase their effectiveness. Although nutritional factors seem to be largely overlooked as potential pharmacological tools for the treatment of depressive disorders, both behavioral changes and mood improvement can be achieved by making up dietary deficiencies.

In a randomized placebo-controlled study of 60 adult participants, Rajizadeh et al. had revealed a decrease in depressive symptoms of the patients with magnesium deficiency (Rajizadeh, Mozaffari-Khosravi, Yassini-Ardakani & Dehghani, 2017). Similarly, Afsharfar et al. had observed a significant change in Beck depression scales but without any significant change in BDNF levels after treatment with magnesium replacement received by participants with depressive complaints (Afsharfar et al., 2021).

While magnesium supplementation appears to have antidepressive effects, at least in rodents and some human populations, high doses of magnesium supplementation can have a variety of side effects, so proper dosing conveys a critical importance. People need to consume magnesium regularly to prevent magnesium deficiency. However, since the recommended daily amount of magnesium varies, it is difficult to accurately determine exactly what the optimum daily intake should be (Song et al., 2005).

Magnesium supplementation is generally well tolerated, but it can occasionally cause gastrointestinal symptoms such as diarrhea, nausea and vomiting. Overdose of intravenous magnesium can cause thirst, hypotension, drowsiness, muscle weakness, respiratory depression, cardiac arrhythmia, coma, and death. Caution should be exercised in patients with renal impairment (Gröber, Schmidt & Kisters, 2015).

Study limitations

Due to the retrospective nature of our study, the patients could not be classified according to the severity of their depressive symptoms. Likewise, most patients included in the study were under at least one antidepressant treatment and the effect of drug use on magnesium levels could not be excluded.

CONCLUSION

Conditions that can lead to hypomagnesemia include alcoholism, uncontrolled diabetes, malabsorption (eg, Crohn's disease, ulcerative colitis, celiac disease, short bowel syndrome, Whipple's disease), endocrine causes (eg, chronic kidney failure, dialysis, Gitelman syndrome), and medications including antibiotics, chemotherapeutic agents, diuretics and proton pump inhibitors (Gröber, 2006).

In our study, the data of 1013 patients were scanned in terms of diabetes, alcoholism and renal failure, and the data of 183 patients were excluded from the study because their serum glucose, GGT and creatinine values were above the reference ranges and the presence of possible causes that could lead to hypomagnesemia.

In conclusion, although contradictory results regarding serum magnesium levels of patients with depressive disorder have been reported in the literature, in our study magnesium deficiency was observed in 11.9% of the patients with depressive disorder, and in accordance with our hypothesis, the mean(±SD) serum magnesium levels of the patients with depressive disorder were statistically significantly different from the population average. The incidence of hypomagnesemia in the general population has been reported to range between 2% and 15% (Gragossian et al., 2022). This information suggests the presence of a close relationship between low serum magnesium levels and also asserts that magnesium deficiency has an important place in the pathophysiology of depression. As of the results of this research study, measurement of serum magnesium levels in patients followed up with a diagnosis of depressive disorder and appropriate supplementation in case of detection of hypomagnesemia is important as it may be effective in reducing depressive symptoms and we thought that our study may contribute to the literature regarding this issue. It is predicted that studies where the clinical course of depressive patients with hypomagnesemia are followed up after magnesium supplementation with reduction of confounding factors to a lowest level will give a better idea about this issue.

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Conflict of Interest
The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions
Plan, design: CC; **Material, methods and data collection:**CC, KS; **Data analysis and comments:** CC, KS; **Writing and corrections:**CC, KS.

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