

Research Article

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INVESTIGATION OF THE RELATIONSHIP BETWEEN HYPOMAGNESEMIA AND INFECTION IN PATIENTS HOUSED IN ONCOLOGY PALLIATIVE CARE CENTER

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Abstract

Objectives: Hypomagnesemia is a serum magnesium (Mg+2) level of <1.8 mg/dl. Hospitalized or critically ill patients, especially cancer patients, are at risk of hypomagnesemia. In the literature, studies on this subject have only been conducted in intensive care units. Therefore, in our study, we aimed to investigate the relationship between serum magnesium levels and infection status in patients with hypomagnesemia admitted to an oncology palliative care center.

Materials and Methods: The age, cancer type, infection status, and biochemical values of 211 patients admitted to the Oncology Palliative Care Service between 01/01/2022 and 31/12/2022 were retrospectively examined. In cases with suspected infection, tests requested by an infectious disease specialist were performed, and according to the results, patients diagnosed with various infections and started on antibiotics were included in the infected group. Data were analyzed using SPSS 25. P values less than 0.05 were considered statistically significant.

Results: The mean age of the participants was determined as 63.41±12.38 years. The mean magnesium (Mg+2) level was measured as 1.82±0.28 mg/dl. Infection was diagnosed in 55.5% of the patients, and the most common infection was a urinary system infection. It was observed that the Mg+2 value was significantly lower in patients with infection than in those without infection (p<0.001). While the frequency of infection was 81.1% in patients with low serum Mg+2 levels, this rate was found to be 29.5% in those without low serum Mg+2 levels.

Conclusion: The statistical relationship observed between hypomagnesemia and infection status in our screened cancer patients suggests that there is a connection between the inflammatory changes caused by the infection and the patient's magnesium levels.

Keywords: Cancer, hypomagnesemia, infection, palliative care.



Introduction

Magnesium (Mg²⁺) is the fourth most abundant element in the human body ($Ca^{2+} > K^+ > Na^+ > Mg^{2+}$) and the second most abundant intracellular cation after potassium. At birth, the human body contains approximately 760 mg of magnesium, which increases to around 5 grams by the age of 4–5 months.¹ The total amount of Mg²⁺ in the body ranges between 20 and 28 grams.² More than 99% of total body magnesium is found in the intracellular compartment, with the majority (approximately 53%) stored in the bones.³ Serum magnesium levels below 1.7–1.8 mg/dL (0.75 mmol/L) are defined as hypomagnesemia.⁴ Magnesium homeostasis is regulated by hormonal mechanisms involving the intestines, bones, and kidneys. Serum Mg²⁺ is filtered by the renal glomeruli and then reabsorbed along the nephron. It is abundantly present in tissues such as the heart, liver, kidneys, skeletal muscles, red blood cells, and the brain.⁵ The MgATP^{2–} complex is essential for the activity of many enzymes. In general, Mg²⁺ acts as a cofactor in all reactions involving the utilization and transfer of ATP, including cellular responses to growth factors and cell proliferation, thus being related to almost every process in the cell.⁶ In addition, Mg²⁺ is vital for maintaining genomic and genetic stability, stabilizing the natural conformation of DNA, and acting as a cofactor for nearly all enzymes involved in nucleotide excision repair, base excision repair, and mismatch repair. Given these effects, low Mg²⁺ levels may be a contributing factor in cancer development.⁷ Some studies have shown a significant relationship between Mg²⁺ and the inflammatory response. These studies observed effects on pro-inflammatory cytokines.⁸

Mg²⁺ deficiency may be associated with the activation of cells such as macrophages, neutrophils, and endothelial cells. In Mg²-deficient rats, macrophages have been found in the peritoneal cavity. These macrophages, considering their histological appearance and reactive oxygen production detected via chemiluminescence activity, appear to be endogenously activated and may partially contribute to increased production of pro-inflammatory cytokines.⁹ One of the most remarkable findings regarding the effects of magnesium deficiency on the organism is the observation of higher levels of apoptosis in the thymus of magnesium-deficient rats compared to controls.¹⁰ A study conducted by Dominguez and colleagues discusses the relationship between Mg²⁺ and infection in the geriatric patient population. It has been shown that magnesium-induced calcium channel blockade plays a role in preventing the release of inflammatory cytokines are a major cause of morbidity and mortality in cancer patients, particularly those with underlying hematological malignancies. Autopsy studies have shown that approximately 60% of deaths are associated with infections.¹²

Hypomagnesemia frequently develops in cancer patients, hospitalized patients, or critically ill individuals, with incidence rates reaching as high as 50–60%.¹³ Factors contributing to the etiology of hypomagnesemia include:



Dietary magnesium deficiency (due to factors such as fasting, protein-calorie malnutrition, total parenteral nutrition)

Factors related to the redistribution of magnesium from the extracellular to the intracellular space (e.g., blood transfusion, acute pancreatitis), gastrointestinal, renal, and transdermal losses. Hypomagnesemia is associated with immune dysfunction, including both acute and chronic infections.¹⁴

In a study evaluating patients diagnosed with sepsis, a significant decrease in serum Mg²⁺ concentrations was observed in patients with acute bacterial infections (bronchopneumonia and urinary tract infections). These changes in Mg²⁺ concentration occurred within a few days, persisted for several weeks, were independent of the bacteria causing the infection, and were not correlated with disease severity. Therefore, this study suggests that measuring serum Mg²⁺ levels may be useful in bacterial infections.¹⁵ Another meta-analysis demonstrated that hypomagnesemia in critically ill patients was associated with an increased incidence of sepsis and prolonged mechanical ventilation.¹⁴ Most studies have been conducted in intensive care units, and there is a lack of research on oncology patients in the terminal phase. Therefore, considering that patients in oncology palliative care centers frequently face infectious diseases, we aimed to investigate the relationship between serum magnesium levels and infection status in this patient group.

Materials and Methods

This retrospective study was conducted using a screening method on 211 patients who were hospitalized in the Oncology Palliative Care Unit between 01/01/2022 and 31/12/2022, after obtaining approval from the Non-Interventional Clinical Studies Ethics Committee on 13/07/2023 with the decision number 2023/06-17. It was determined that the sample size was appropriate based on power analysis. Demographic data, medical records, biochemical results, infection status, and outcomes of the patients were collected through the hospital information management system and analyzed. Since CRP (C-reactive Protein) levels may be directly affected by malignancy, CRP values were excluded from the data. According to the hospital laboratory, reference ranges for biochemical parameters were determined as follows: magnesium 1.8–2.6 mg/dL, white blood cells (WBC) $4.2-10.6 \times 10^3/\mu$ L, procalcitonin 0–0.065 ng/mL.

Inclusion criteria for the study were being over the age of 18 and having a diagnosis of malignancy. Patients who stayed in the hospital for less than 24 hours, those who were not tested for serum magnesium, complete blood count, or procalcitonin at admission, patients who had received chemotherapy in the last month, those with hematological malignancies, chronic kidney failure, corticosteroid use, or who did not meet the inclusion criteria were excluded from the study. Patients receiving corticosteroid therapy and those with hematologic malignancies were excluded because such conditions may directly affect leukocyte levels.



In our hospital, an infectious diseases consultation is required to initiate antibiotic therapy. Therefore, patients with clinical signs of infection or suspected infection based on laboratory findings such as WBC, procalcitonin, or culture results were referred to the infectious diseases department. The tests requested by the infectious diseases specialist were performed, and based on the results, various infection diagnoses were made, and antibiotic therapy was initiated. These patients were classified as the infected group.

Statistical Analysis

Descriptive statistics such as frequency, percentage, mean, and standard deviation were used in the data analysis via the SPSS 22.0 software package. Relationships between categorical parametric variables were examined using Pearson Chi-Square and Fisher's Exact Test, while the relationship between scale scores and categorical variables was investigated using the Independent Samples t-test and One-Way ANOVA. The results were evaluated at a 95% confidence interval. A p-value of less than 0.05 was considered statistically significant.

Results

After screening through the hospital information management system and excluding patients who met the exclusion criteria, a total of 211 individuals were included in the study. The demographic data of the participants and the distribution of cancer types are presented in Table 1.

The levels of Mg²⁺, WBC, and procalcitonin of the participants were analyzed. The mean magnesium level was determined as 1.82±0.28 mg/dL. Magnesium, leukocyte, and procalcitonin values are presented in Table 2. According to the grouping based on infection status, 94 patients (44.5%) were found to have no infection. The most frequently observed infection was urinary tract infection in 44 patients (20.9%), followed by pneumonia, which was also detected in 44 patients (20.9%) (Figure 1).



Table 1. Distribution of demographic data and cancer groups among participants.

Variables	Mean	SD
Age	63.41	12.38
Gender	n	%
Female	107	50.7
Male	104	49.3
Cancer Type		
Gastric Cancer	24	11.4
Breast Cancer	21	10
Oropharyngeal Cancer, Laryngeal Cancer, Tongue Base Cancer	20	9.5
Lung Cancer	17	8.1
Pancreatic Cancer	15	7.1
Endometrial Cancer	14	6.6
Colon Cancer	14	6.6
Brain Cancer	13	6.2
Rectal Cancer	13	6.2
Cervical Cancer	12	5.7
Prostate Cancer	9	4.3
Nasopharyngeal Cancer	8	3.8
Esophageal Cancer	6	2.8
Other	6	2.8
Ovarian Cancer	5	2.4
Liver Cancer	5	2.4
Biliary Tract Cancer	3	1.4
Bladder Cancer	3	1.4
Kidney Cancer	3	1.4
Head and Neck Region	44	20.9
Supradiaphragmatic	45	21.3
Infradiaphragmatic	122	57.8



Table 2. Magnesium, WBC, and procalcitonin levels

	Unit	Mean	SD
Magnesium	mg/dL	1.82	0.28
WBC	10 ³ /mikroL	8877.25	4472.96
Procalcitonin	Procalcitonin ng/mL		0.49**



Figure 1. Distribution of Infection Types Among Patients

A comparison was made between magnesium, leukocyte (WBC), and procalcitonin levels and the infection status of the patients. Significant differences were observed in WBC and procalcitonin levels between infected and non-infected patients (p<0.001, p<0.001) (Table 3).

When grouped according to participants' gender, no statistically significant differences were found in magnesium, leukocyte (WBC), and procalcitonin levels (Table 4).

When magnesium levels were examined according to different types of infections, the mean Mg^{2+} level in patients with urinary tract infections was found to be 1.7 ± 0.28 mg/dL. Significant differences were found in mean Mg^{2+} levels among different infection types (p<0.001) (Table 5).



Table 3. Comparison of magnesium, WBC, and procalcitonin levels according to the presence of infection

		None (94)		Present (117)		_
	Unit	Mean	SD	Mean	SD	p-value
Magnesium	mg/dL	1.95	0.2	1.72	0.29	<0.001
WBC	10 ³ /mikroL	7632.97	3365.04	9876.92	4987.92	<0.001
Procalcitonin	ng/ml	0.052*	0.11**	0.368*	1.13**	<0.001***

*Median, **IQR, ***Mann-Whitney U test p-value less than 0.05 were considered significant

Table 4. Comparison of magnesium, WBC, and procalcitonin levels according to gender

			-			
		Female		Male		_
	Unit	Mean	SD	Mean	SD	p-value
Magnesium	mg/dL	1.8	0.27	1.84	0.28	0.896
WBC	10 ³ /mikroL	8340.18	4478.01	9429.8	4421.21	0.56
Procalcitonin	ng/ml	0.135*	0.44**	0.165*	0.49**	0.144***

*Median, **IQR, ***Mann-Whitney U test p-value less than 0.05 were considered significant



	n	Unit	Mean	SD	p-value
No infection	94	mg/dL	1.95	0.2	<0.001*
Urinary tract					
infection	44	mg/dL	1.7	0.28	
Catheter infection	9	mg/dL	1.89	0.17	
Pneumonia	44	mg/dL	1.71	0.29	
Soft tissue infection	14	mg/dL	1.72	0.32	
Acute					
gastroenteritis	6	mg/dL	1.72	0.4	

Table 5. Comparison of Mg levels according to infection types

*P-values less than 0.05 were considered significant

Table 6. Comparison of infections according to magnesium level

-	Normomagnesemia (1,8-2,6 mg/dL)		Hypomagnesemia (<1,8 mg/dL)		
infection	n	%	n	%	p-value
None	74	70.5	20	18.9	<0.001*
Present	31	29.5	86	81.1	

* P-values less than 0.05 were considered significant

According to the hospital laboratory reference values, levels below 1.8 mg/dL were considered suggestive of hypomagnesemia. When patients were grouped as hypomagnesemic and normomagnesemic, the frequency of infection was found to be significantly higher among patients with hypomagnesemia (p<0.001, Table 6). In the analysis of procalcitonin levels according to magnesium status, the median procalcitonin level was found to be 0.091 ng/mL in patients with normal magnesium levels, whereas it was 0.215 ng/mL in patients with low magnesium levels. A significant increase in procalcitonin levels was observed in patients with low magnesium levels (p<0.001) (Figure 2).





Figure 2. Procalcitonin Levels According to Magnesium Status

Discussion

In our study, cancer types were compared among patients admitted to the oncology palliative care center. While subdiaphragmatic cancers were frequently detected, the most common cancer type was gastric cancer. This was followed by breast and pharyngeal region tumors. Lung cancer ranked third. Although there are similarities between the most frequently encountered cancers in our study and those observed in the literature, the main reason for the lack of complete alignment is thought to be that the clinic where the study was conducted provides diagnosis and treatment services to advanced-stage cancer patients who require hospitalization.

In a study conducted in the USA, it was observed that the majority of cancer patients aged 30 and older were women, and this trend continued in the geriatric age group.¹⁶ In our study, the mean age of the included patients was found to be 63.41 ± 12.38 years. The majority of the participants were female patients. Compared to studies in the literature, we observed that female dominance was consistent with the literature. Infection is a significant cause of morbidity and mortality in cancer patients. Autopsy series of patients with hematologic malignancies have reported infection rates of 60%. In patients with solid organ tumors, this rate was found to be 50%.¹⁷

In a study by Elfaituri et al., which investigated infection-related cancer deaths between 1973 and 2014, 141,440 cancer patients were retrospectively analyzed, and the most commonly identified infections were pneumonia and influenza along with sepsis. Prostate cancer was identified as the most common disease associated with infection-related deaths.¹⁸ In a study by Zheng et al., infection-related deaths among cancer patients in the United States were examined. Although pneumonia-related deaths were the most common, sepsis was observed as the second most important cause.¹⁹ In our study, the most frequently observed infections were urinary tract infections (20.9%) and pneumonia (20.9%). As seen in the literature, pneumonia, the most frequently observed infectious agent in cancer patients, was similarly identified in our study.^{18,19}



Oncological conditions are among the leading causes of death worldwide. According to the 2021-2022 data in our country, they are seen as the second most important cause of death with 14% and 15.2%, respectively.²⁰ In the geriatric population, cancer and cancer-related conditions significantly contribute to mortality. Cancerrelated conditions may account for up to 70% of the observed mortality in this patient group.²¹ According to WHO GLOBOCAN 2022 data, the most common cancer types in geriatric patients worldwide are breast, lung, and colorectal cancers in women; and prostate, lung, and colorectal cancers in men. According to the WHO's incidence projections made in 2020, lung, prostate, and colorectal cancers are predicted to be the most prevalent cancers by 2045.²² In our study, while no difference was observed in magnesium levels between genders, magnesium levels were found to be significantly lower in patients with infections compared to those without. The frequency of infection in patients with hypomagnesemia was 81.1%, while it was 29.5% in those without hypomagnesemia, demonstrating that hypomagnesemia significantly increases the risk of infection. While there was no significant difference between hypomagnesemia and WBC, patients with low magnesium levels had significantly higher procalcitonin levels. In our study, increased procalcitonin levels were observed in association with inflammation due to infection, and the development of hypomagnesemia was also observed, consistent with the literature. In a prospective observational study conducted by Limaye et al. on 100 adult ICU patients, hypomagnesemia was detected in 52% of patients admitted to the ICU, and an increase in sepsis incidence and mortality was reported in patients with hypomagnesemia.¹⁴ In another study, a significant relationship was found between hypomagnesemia and high levels of C-reactive protein (CRP) and procalcitonin in pediatric intensive care units.²³ Magnesium is required for steps related to cell growth. It is essential at every stage, from receptor-mediated intracellular signaling and transphosphorylation reactions to gene transcription, protein synthesis, DNA replication, and cell division.²⁴ One study showed that serum magnesium levels frequently decreased in patients with solid tumors, and decreased independently of treatments, and this decrease was associated with the stage of the malignant tumor.²⁵

In a study by Marciniak et al., it was stated that magnesium levels could be used as a biomarker in the identification of cancers and that impaired magnesium levels should be evaluated as a cancer trigger.²⁶ In a meta-analysis examining electrolyte disturbances in patients with solid tumors treated with anti-EGFR monoclonal antibodies, colorectal cancer patients receiving anti-EGFR monoclonal antibody treatment showed the highest risk of electrolyte imbalance compared to their controls. In addition, colorectal cancer patients receiving panitumumab were shown to be more susceptible to severe hypomagnesemia.²⁷ In a study conducted in mice, magnesium chloride supplementation was observed to reduce the expression of inflammation-related genes such as TNF- α and TGF- β 1 and slow tumor progression.²⁸ In a randomized clinical study, oral magnesium supplementation in children receiving cisplatin-based chemotherapy was shown to reduce febrile neutropenia (FN) attacks by 47% and also decrease the incidence of septic shock.²⁹ In another study, the use of magnesium sulfate in critically ill patients with sepsis was associated with a lower all-cause mortality rate in 28-day follow-up.³⁰



These findings suggest that magnesium may support the immune system with its anti-inflammatory effects and provide protection against infections.

Limitations

This study was conducted retrospectively. While a prospective and multicenter design provides advantages in terms of patient distribution and data evaluation, retrospective analyses may offer an opportunity to reach a broader group for the interpretation of findings. Our study was conducted with a limited sample of oncology palliative care patients, and patients using diuretics could not be excluded due to the widespread use of diuretics in this population. The laboratory values at the time of patient admission were included in the study. To clarify the relationship between hypomagnesemia and infection and to exclude all potential causes of hypomagnesemia, prospective studies are needed. However, consistent with the literature, our study demonstrated a link between Mg²⁺ and infection in oncology palliative care patients.

In conclusion, a total of 211 participants were included in our study, 50.7% of whom were female, with a mean age of 63.41 ± 12.38 years. Among the participants, the most common type of cancer was gastric cancer, followed by breast and laryngeal cancers. The most frequently observed cancer types were located below the diaphragm.

While no infection was detected in 44.5% of the participants, pneumonia was present in 20.9% and urinary tract infection in 20.9%. The magnesium levels in patients diagnosed with infection were found to be significantly lower compared to those without infection. Although there was no significant change in white blood cell count in patients with hypomagnesemia, procalcitonin levels were significantly higher, and hypomagnesemia was more frequently observed in the presence of infection. Given its role in enzymatic reactions and nuclear functions, magnesium may serve as a biomarker associated with inflammation in cancer patients. A relationship was observed between inflammation-related changes caused by infection and magnesium levels in patients. Serum magnesium levels should be monitored in the follow-up of oncological patients. If magnesium levels are low, patients should be evaluated for infections. Even in the absence of infection, magnesium replacement should be considered, as hypomagnesemia may potentially increase the risk of infection. More comprehensive studies with larger sample sizes are needed to evaluate the effect of hypomagnesemia on infection development and the impact of magnesium replacement in cancer patients.

Ethical Considerations: The local ethics committee approval numbered 2023/06-17 was obtained from the Ethics Committee of the University of Health Sciences Tepecik Education and Research Hospital.

Conflict of Interest: The authors declare no conflict of interest.



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