



Original Research / Orijinal Araştırma

Knowledge and Behaviors of Family Physicians and Internal Medicine Physicians Regarding the Use of Magnesium for Supplementation and Treatment

Aile Hekimleri ve İç Hastalıkları Hekimlerinin Takviye ve Tedavi Amaçlı Magnezyum Kullanımına İlişkin Bilgi ve Davranışları

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Abstract

Objective: To identify indications for magnesium use and assess physicians' knowledge of different formulations of magnesium in medication and supplements

Method: A descriptive study was conducted online via Google Forms between January 18 and April 20, 2023. The study population consisted of family physicians (general practitioners, residents, and specialists) and internal medicine physicians (residents and specialists) in Ankara. All physicians were attempted to be reached, and no sampling calculation was made. The survey consisted of 15 questions.

Results: A total of 119 physicians completed the survey. The mean age of the physicians who participated in our study was 30.47±4.94 years (min=25, max=48) and 62.2% were female. Of them, 69.7% were family physicians, 30.3% were internal medicine physicians, 77.3% were research assistants and 22.7% were specialists. The most common indications for magnesium treatment were muscle cramps (89.1%) and hypomagnesemia (87.4%); the most commonly used preparations were magnesium oxide (79.8%) and magnesium sulfate (32.8%). The most common indications of using magnesium were cramps (32.4%) and insomnia (13.5%); the most frequently used preparations were magnesium oxide (26.3%), magnesium citrate+malate+glycinate (13.1%), and magnesium biglycinate (13.1%). Physicians who had been practicing for more than 5 years prescribed magnesium more (p=0.010), recommended magnesium supplements more (p=0.020), and used magnesium supplements themselves more (p=0.025) than physicians who had been practicing for 5 years or less. It was found that specialists questioned patients' use of vitamin-mineral supplements more (p=0.044) and recommended magnesium supplements more (p=0.001) than residents. It was found that family physicians prescribed the magnesium used by patients more (p<0.001) and recommended more magnesium-rich nutrition to patients (<0.001) than internal medicine physicians.

Conclusion: The physicians who participated in our study preferred magnesium forms covered by social security institution reimbursement for their patients, whereas they preferred forms with higher bioavailability for their own use. It was observed that family physicians provided more magnesium-rich dietary recommendations and prescribed the magnesium used by the patients than internal medicine physicians.

Keywords: Magnesium, nutrition, dietary supplement

Özet

Amaç: Bu çalışmanın amacı, aile hekimleri ve iç hastalıkları hekimlerinin magnezyum kullanım endikasyonlarını ve hekimlerin magnezyum preparatlarının içerdiği magnezyum formlarına ilişkin bilgi ve davranışlarını belirlemektir.

Yöntem: Tanımlayıcı tipteki çalışmamız 18 Ocak 2023 ile 20 Nisan 2023 tarihleri arasında Google-Forms üzerinden online olarak gerçekleştirilmiştir. Araştırmanın evrenini Ankara'daki aile hekimleri (pratisyen, asistan ve uzmanlar) ve iç hastalıkları hekimleri (asistan ve uzmanlar) oluşturmuştur. Araştırmamızda tüm hekimlere ulaşılmaya çalışılmış olup, örneklem hesaplaması yapılmamıştır. Anketimizde 15 soru bulunmaktadır.

Bulgular: Çalışmamıza katılan hekimlerin yaş ortalaması 30.47±4.94 yıl (min=25, max=48) ve %62.2'si kadındı. Katılımcıların %69,7'si aile hekimi, %30,3'ü iç hastalıkları hekimi, %77,3'ü araştırma görevlisi ve %22,7'si uzman hekimdi. Magnezyum tedavisi için en yaygın endikasyonlar kas krampları (%89,1) ve hipomagnezemi (%87,4), en yaygın kullanılan preparatlar ise magnezyum oksit (%79,8) ve magnezyum sülfat (%32,8) idi. Kendisi magnezyum kullanan hekimler en sık kramp (%32,4) ve uykusuzluk (%13,5) endikasyonları ile, en sık magnezyum oksit (%26,3), magnezyum sitrat+malat+glisinat (%13,1) ve magnezyum biglisinat (%13,1) preparatlarını kullanmaktaydı. Beş yıldan uzun süredir çalışan hekimler, beş yıl veya daha kısa süredir çalışan hekimlere kıyasla hastalara daha sık magnezyum reçete etmekte (p=0,010), hasta ve yakınlarına daha sık magnezyum takviyesi önermekte (p=0,020) ve kendileri daha sık magnezyum takviyesi kullanmaktaydı (p=0,025). Uzman hekimlerin asistan hekimlere kıyasla hastaların vitamin-mineral takviyesi kullanımını daha fazla sorguladığı (p=0,044) ve hastalarına daha fazla magnezyum takviyesi önerdiği (p=0,001) tespit edildi. Aile hekimlerinin hastaların kullandığı magnezyumu, dahiliye hekimlerine göre daha fazla reçete ettiği (p<0,001) ve hastalara magnezyumdan zengin beslenmeyi ile ilgili daha çok bilgi verdiği (<0,001) bulundu.

Sonuç: Çalışmamıza katılan hekimler, hastaları için sosyal güvenlik kurumu geri ödeme kapsamında olan magnezyum preparatlarını tercih ederken, kendi kullanımları için biyoyararlanımı daha yüksek olan formları tercih etmişlerdir. Aile hekimlerinin dahiliye hekimlerine göre hastalarına daha fazla magnezyumdan zengin beslenme önerilerinde buldukları ve hastaların kullandığı magnezyumu daha sık reçete ettikleri görülmüştür.

Anahtar Kelimeler: Magnezyum, beslenme, besin takviyesi.

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Introduction

Magnesium is a vital element which is involved in various functions almost all organs and systems in the human body. Magnesium has a regulatory role in more than 300 enzyme systems. Some of its important functions in the human body are listed below:

- Synthesis functions: Protein synthesis, DNA-RNA synthesis, glutathione synthesis,
- Muscle and nerve functions by controlling the passage of calcium and potassium across cell membranes,
- Regulation of blood sugar by glycolysis, and oxidative phosphorylation,
- Synthesis and regulation of vitamin D and parathormone,
- Control of bone formation through its role in osteoblast and osteoclast functions,
- Regulation of blood pressure,
- Playing role in neurotransmitter synthesis and release,
- Presence in the structure of ATP.¹

Magnesium is naturally found in green leafy vegetables, unprocessed grains, nuts, and seeds.² Over time, the consumption of magnesium in diets has declined, largely due to poor dietary choices like processed foods and animal products, as well as insufficient intake of vegetables, seeds, and whole grains. Based on the National Health and Nutrition Examination Survey (NHANES) 2013-2016, about 48% of the United States population do not meet the recommended daily magnesium intake.³ Similarly, according to the recent Türkiye Ministry of Health Türkiye Nutrition Guide (TÜBER) 2022, nearly half of the population in Türkiye is unable to fulfill their daily magnesium requirements through dietary intake alone.⁴

The consumption of dietary supplements has surged in recent years, particularly in response to health worries stemming from the COVID-19 pandemic. This increase can be attributed to targeted advertising and social media campaigns. According to a report from the Food Supplement and Nutrition Association, sales of minerals and dietary supplements have risen by 140% on a weekly basis since March 2020.⁵ Before the pandemic, 13% of the population in Türkiye used dietary supplements, but this number increased to 27% during the pandemic period, according to survey studies. The prevalence of supplementary food use in Türkiye has been found to range between 13% and 66% in different studies.⁶ There has been an increase in the use of magnesium supplements, along with other supplements, during this period. Despite the limited level of evidence, magnesium supplements are suggested for various conditions, including insomnia, blood glucose regulation, depression, migraine, restless leg, and premenstrual syndrome. According to a study, physicians were the primary source of information about which supplement to use before and during the COVID -19 pandemic.⁷ In order to uphold physicians as the primary source of information regarding dietary supplements, it is crucial to ensure that they maintain high levels of awareness and knowledge. This is especially vital for internal medicine and family physicians, who regularly engage with the general adult population. With the increasing use of dietary supplements, it is essential for these healthcare providers to remain well-informed and current. Internal medicine and family physicians bear the important responsibility of striking a balance between safeguarding society from potential harms of supplements and ensuring that individuals are not deprived of potential benefits.

This study aimed to identify indications for magnesium use and assess physicians' knowledge of different formulations of magnesium in medication and supplements.

Methods

The descriptive study was conducted with family physicians and internal medicine physicians online via Google Forms between January 18, 2023 and April 20, 2023. The population of the study consisted of family physicians (general practitioners, residents, and specialists) and internal medicine physicians (residents and specialists) in Ankara, Türkiye. The survey link, which included the necessary permissions, was sent to social media groups including general practitioners, family medicine residents, specialists; internal medicine residents and specialists in Ankara.

In our study, all physicians were attempted to be reached, because the correct number of our population (family physicians and internal medicine physicians working in Ankara) could not be reached so we were unable to make a sample calculation. Representativeness was not aimed in this study. Those who engaged with the survey via survey link and agreed to answer were included in the study.

The inclusion criteria were being a family physicians (general practitioner, resident, or specialist) or an internal medicine physician (resident or specialist), actively practicing, and answering all questions in the survey.

Research data were collected online with a 15-question questionnaire. The questions were developed in light of the literature. In the first part of the survey, demographic characteristics of physicians such as age and gender; in the

second part, professional characteristics such as the number of years of professional experience, specialization status, and specialities were questioned. In the last part of the questionnaire, questions were asked to determine the behaviors of physicians regarding magnesium supplementation and treatment.

The questionnaire was conducted via Google Forms. At the beginning of the questionnaire, the informed consent was obtained.

Statistical Analysis

The data obtained in the study were transferred to electronic media (data entry) and statistical analyses of the data were performed by using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp. Released 2015. Armonk, NY: IBM Corp) statistical computer package program licensed by Hacettepe University.

In the analyses, descriptive statistics were expressed as distributions, percentages, means, minimum-maximum values, and standard deviations. For categorical variables, Pearson's Chi-square test was used to evaluate whether there was a difference between the groups, and Fisher's exact test was used when necessary in a 2x2 arrangement. A p value of <0.05 was considered statistically significant.

Ethics committee approval

The ethics committee approval was obtained from Hacettepe University Non-interventional Clinical Research Ethics Committee on March 07, 2023 with decision number of 2023/04-17.

Results

One hundred and nineteen participants were included, the mean age of the physicians was 30.47 ± 4.94 years (min=25; max=48) and 62.2% were female. Other professional characteristics of the participants are shown in Table 1.

Table 1. Occupational characteristics of the physicians

Occupational characteristics		n	%
Years in profession (year)	≤4	58	48.7
	5-9	45	37.8
	10-14	8	6.7
	≥15	8	6.7
Title	Research assistant	92	77.3
	Specialist	27	22.7
Specialty	Family medicine	83	69.7
	Internal medicine	36	30.3

Among the participants, 33.6% used magnesium supplements (Figure 1).

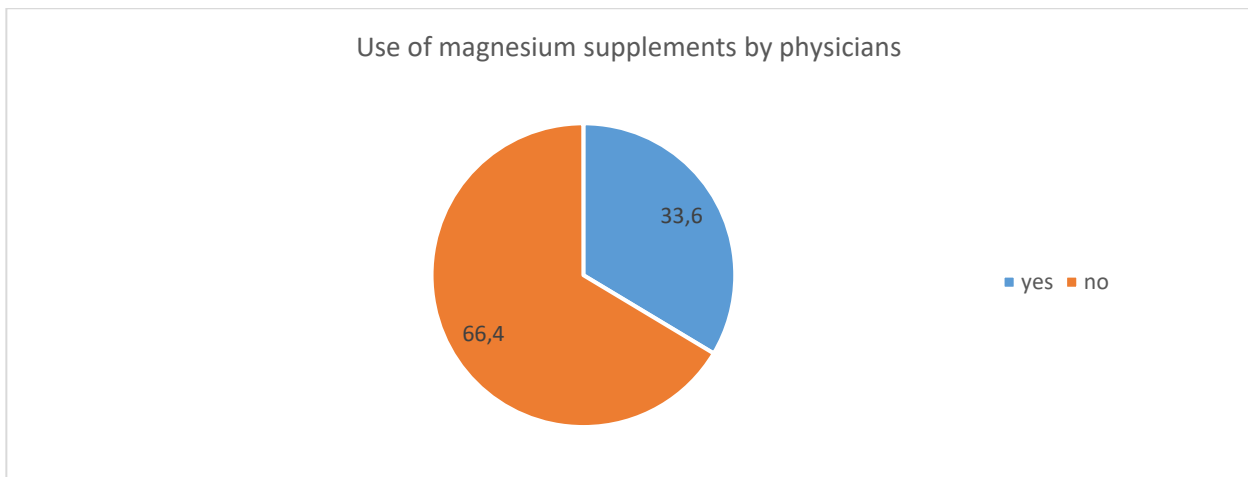


Figure 1. Frequency of magnesium supplement use by physicians

Specialists reported obtaining information on magnesium use from congresses more frequently than other physicians ($p=0.002$). On the other hand, internal medicine physicians mentioned obtaining more information about magnesium use from residency training compared to family physicians ($p<0.001$). Additionally, internal medicine physicians reported using social media and television programs as the sources of information on magnesium use less often than family physicians ($p=0.003$).

Of the physicians, 48.7% believe that people's magnesium intake through their diet is inadequate due to current societal dietary habits. Of them, 37% are unsure about the adequacy of magnesium intake, while only 14.3% believe that it is sufficient. 16% of physicians reported that they do not provide magnesium-rich dietary recommendations to their patients, citing a lack of knowledge on the topic. For those who do offer recommendations for magnesium support, nuts (especially almonds) are suggested 31.1% of the time, followed closely by bananas at 29.4% (Figure 2).

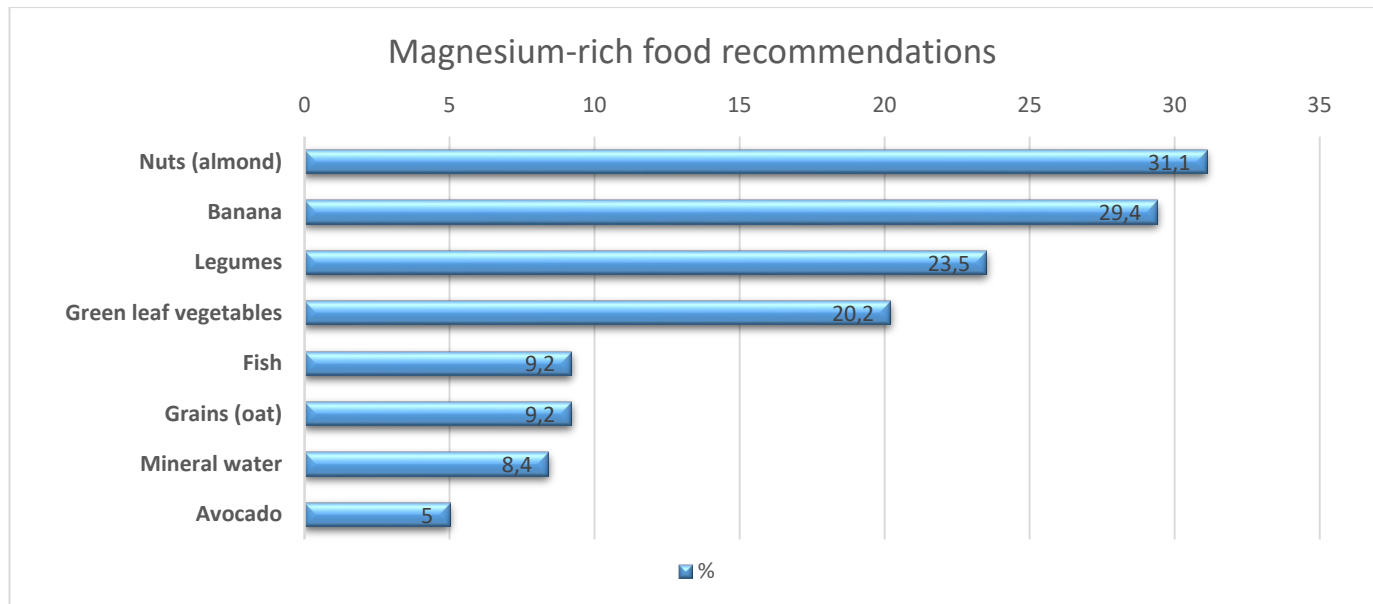


Figure 2. Percentage and distribution of foods recommended by physicians

The data in Table 2 illustrates the prevalence of indications for magnesium use among physicians who prescribed magnesium treatment. The most frequent indications for prescribing magnesium treatment were muscle cramps (89.1%) and hypomagnesemia (87.4%). The most prevalent reasons for recommending magnesium supplementation were increasing exercise capacity (54.6%) and managing insomnia (38.7%). Among physicians who used magnesium supplements themselves, the primary reasons were muscle cramps (32.4%) and insomnia (13.5%).

Table 2. *Distribution of behaviours of physicians related with indications for magnesium*

Indications for magnesium treatment		
Indication	%	n
Muscle cramps	89.1	106
Hypomagnesemia	87.4	104
Constipation	50.4	60
Restless leg syndrome	41.2	49
Migraine	24.4	29
Arrhythmia	16.8	20
Chronic obstructive pulmonary disease	15.1	18
Asthma attack	12.6	15
Eclampsia	9.2	11
Gastroesophageal reflux/ Gastritis	6.7	8
Indications for magnesium supplements		
Indication	%	n
Enhancing exercise capacity	54.6	65
Insomnia	38.7	46
Premenstrual syndrome	37.8	45
Depression	31.9	38
Prevention of osteoporosis	26.1	31
Regulation of hypertension	10.9	13
None	10.9	13
Regulation of blood glucose	5.9	7
Indications for the use of magnesium supplements by doctors for themselves		
Indication	%	n
Muscle cramps	32.4	12
Insomnia	13.5	5
Mood disorder (depression)	10.8	4
Enhancing exercise capacity	10.8	4
Restless leg syndrome	8.1	3
Migraine	8.1	3
Dysmenorrhea	5.4	2
Constipation	2.7	1
Regulation of hypertension	2.7	1
Brain fog	2.7	1
Premenstrual syndrome	2.7	1
More than one answer could be chosen.		

Table 3 shows the distribution of magnesium preparations recommended by physicians to their patients and the preparations used by physicians who themselves take magnesium supplements. It was found that magnesium oxide was the most frequently recommended preparation (79.8%), followed by magnesium sulfate (32.8%), and magnesium carbonate (30.3%). On the other hand, physicians who take magnesium supplements themselves predominantly used magnesium oxide (26.3%) and a combination of magnesium citrate, malate, and glycinate (13.1%).

Table 3. *Distribution of behaviours of physicians related with magnesium preparations*

Distribution of magnesium preparations recommended to patients by physicians		
Magnesium (Mg) preparation	%	n
Mg oxide	79.8	95
Mg sulphate	32.8	39
Mg carbonate	30.3	36
Mg citrate	21.0	25
Mg citrate + pyridoxine	18.5	22
Mg citrate + malate + glycinate	17.6	21
Mg malate + biglycinate + acetyltaurate	14.3	17
Mg L-theronate	7.6	9
Mg-malate	5.9	7
Mg-biglycinate	4.2	5
Mg-aspartate	1.7	2
Distribution of magnesium preparations used by physicians for themselves		
Mg preparation	%	n
Mg oxide	26.3	10
Mg citrate + malate + glycinate	13.1	5
Mg biglycinate	13.1	5
Mg citrate	7.8	3
Mg carbonate + oxide	7.8	3
Mg malate	5.2	2
Mg malate + biglycinate + acetyl taurate	2.6	1
Mg citrate + pyridoxine	2.6	1
Mg carbonate	2.6	1
Not specified	18.4	7
More than one answer could be chosen.		

When analyzing the behaviors of physicians regarding the use of magnesium, it was found that female physicians were more likely to believe that adequate magnesium intake could not be obtained through diet compared to male physicians ($p=0.009$). However, no statistically significant difference was found between genders regarding other magnesium-related behaviors.

Table 4 provides a detailed breakdown of physicians' behaviors regarding magnesium use based on the duration of their practice, their specialty status, and their specialty field.

Regarding the duration of physicians' practice, those who had been practicing for more than 5 years were found to prescribe magnesium more frequently ($p=0.010$), recommend magnesium supplements to their patients and relatives more often ($p=0.020$), and use magnesium supplements themselves more often ($p=0.025$) compared to physicians who had been practicing for 5 years or less.

The study also examined the attitudes of physicians towards the use of magnesium supplements based on their specialty status and specialty field. It was found that specialist physicians were more likely to recommend magnesium supplements compared to residents ($p=0.001$). Additionally, specialist physicians were more likely to question their patients about the use of vitamin-mineral supplements ($p=0.044$) and recommend magnesium supplements to both their patients and their relatives more frequently ($p=0.001$). However, there was no significant difference in the use of magnesium supplements based on the specialty status of the physicians ($p>0.05$).

The study found that family physicians were more likely to prescribe magnesium supplements that the patient was already using ($p<0.001$) and provide more magnesium-rich nutrition recommendations to patients ($p<0.001$) compared to internal medicine physicians. However, there was no significant difference in the use of magnesium supplements based on the branches of physicians ($p>0.05$).

Table 4. Physicians' behaviors regarding magnesium use according to practicing time as a physician, their specialty status, and their specialty field

		Working time as a physician				p	Specialty status				p	Specialty field				p
		≤5 years		>5 years			Residents		Specialist			Family Medicine		Internal Medicine		
		%	n	%	n		%	n	%	n		%	n	%	n	
Status of prescribing the magnesium that the patient is using	No	13.2	10	2.3	1	0.010	10.9	10	3.7	1	0.180	4.8	4	19.4	7	<0.001
	Yes	26.3	20	51.2	22		38.0	35	25.9	7		45.8	38	11.1	4	
	Sometimes	60.5	46	46.5	20		51.1	47	70.4	19		49.4	41	69.4	25	
Status of questioning the vitamin and mineral supplements used by the patient	No	10.5	8	11.6	5	0.317	14.1	13	0.0	0	0.044	12.0	10	8.3	3	0.610
	Yes	38.2	29	51.2	22		38.0	35	59.3	16		44.6	37	38.9	14	
	Sometimes	51.3	39	37.2	16		47.8	44	40.7	11		43.4	36	52.8	19	
Do you think people get enough magnesium from food?	No	44.7	34	55.8	24	0.467	45.7	42	59.3	16	0.377	51.8	43	41.7	15	0.245
	Yes	14.5	11	14.0	6		14.1	13	14.8	4		10.8	9	22.2	8	
	No idea	40.8	31	30.2	13		40.2	37	25.9	7		37.3	31	36.1	13	
Status of recommendation of magnesium supplementation to patients/relatives	No	42.1	32	20.9	9	0.020	42.4	39	7.4	2	0.001	31.3	26	41.7	15	0.276
	Yes	57.9	44	79.1	34		57.6	53	92.6	25		68.7	57	58.3	21	
Status of magnesium supplementation use	No	73.7	56	53.5	23	0.025	69.6	64	55.6	15	0.175	62.7	52	75.0	27	0.190
	Yes	26.3	20	46.5	20		30.4	28	44.4	12		37.3	31	25.0	9	
Status of giving magnesium rich nutrition recommendations to patients	No	18.4	14	11.6	5	0.331	18.5	17	7.4	2	0.167	4.8	4	41.7	15	<0.001
	Yes	81.6	62	88.4	38		81.5	75	92.6	25		95.2	79	58.3	21	

Chi-square test was used.

Discussion

The purpose of the study was to assess the knowledge and practices of family physicians and internal medicine physicians in recommending and using magnesium supplements. The study found that magnesium was commonly used for treating muscle cramps and hypomagnesemia, and the most common reasons for supplementation were increased exercise capacity and insomnia. Physicians who used magnesium supplements themselves also reported using them for muscle cramps and insomnia. The most frequently recommended magnesium preparations were magnesium oxide, magnesium sulphate, and magnesium carbonate. Meanwhile, physicians who personally took magnesium supplements commonly used magnesium oxide and a combination of magnesium citrate, malate, and glycinate.

Our study found that family physicians tend to give their patients more dietary recommendations rich in magnesium compared to internal medicine physicians. The reason for this result might be about the biophysicosocial approach of family physicians, especially the disease management aspects of family physicians include both treatment and lifestyle change recommendations, so in daily practice, they might spend more time for lifestyle recommendations, such as diets. However, 16% of the physicians participating in the study admitted to having no knowledge about magnesium-rich foods and did not discuss the matter with their patients. According to TÜBER 2022, 49% of the population in our country does not receive the daily requirement of magnesium, which is essential for optimum health.⁴ As people age, the rate of not meeting the daily magnesium requirement with diet increases to 67% over the age of 65 and 75% over the age of 75.⁴ This highlights the importance of providing magnesium-rich dietary recommendations and even considering the use of magnesium supplements, particularly among the elderly population. It is crucial for all physicians to have knowledge about this issue and to educate their community, especially in terms of preventive medicine.

According to TÜBER 2022, foods that are high in magnesium include whole grains, dried legumes, nuts, green vegetables, milk, and dark chocolate.⁴ In 2015, the US Food and Agriculture Research Service listed pumpkin seeds (156 mg), chia seeds (111 mg), almonds (80 mg), spinach (78 mg), cashews (74 mg), peanuts (63 mg), and soy milk (61 mg) as the top foods that are rich in magnesium per serving.⁸ Our study found that after nuts (especially almonds), bananas were recommended second most frequently with a 29% recommendation rate. However, one serving of banana with a magnesium content of 30 mg falls in the middle of the list of magnesium-rich foods. In general, 9.2% of the participating physicians in our study recommended fish and seafood as magnesium-rich foods. However, seafood other than salmon is not considered a magnesium-rich diet.⁸ The magnesium-rich dietary recommendations given by the participating physicians in our study align with the aforementioned nutrition guidelines. It is imperative to increase the knowledge of physicians about magnesium-rich foods or to raise their awareness about referring their patients to a dietician for nutrition education.

The physicians who participated in our study reported that they most frequently used magnesium oxide (79.8%) and magnesium sulphate (32.8%) for their patients. These two forms are believed to be more popular among physicians and patients because they are available through government health insurance reimbursement. When the physicians' own magnesium supplements were examined, magnesium oxide was the most commonly used form. Additionally, it was found that physicians preferred preparations containing magnesium biglycinate and magnesium citrate+malate+glycinate combination for their own use, even though they were not covered by insurance, more than those prescribed for their patients.

In our study, we noticed that only a small number of physicians recommended magnesium supplements other than magnesium oxide and sulphate. However, magnesium oxide, which contains the highest amount of elemental magnesium, has low intestinal bioavailability (only 10%) and can cause more laxative side effects.^{9,10} On the other hand, magnesium citrate is affordable and has relatively high bioavailability (25-30%).¹¹ Magnesium forms that are bound to amino acids like magnesium aspartate and taurate are generally more bioavailable than magnesium oxide but less bioavailable than magnesium citrate.¹² Unlike other magnesium supplements, magnesium biglycinate is highly bioavailable because it is absorbed from different areas of the intestines.¹³

While magnesium therapy is commonly used for conditions such as muscle cramps, constipation, restless leg syndrome, it has also been identified as a potential treatment for insomnia,¹⁴ premenstrual syndrome,¹⁵ insulin resistance, and glycemic control. According to a randomized controlled study conducted by El-Derawi et al. in 2018, patients with type 2 diabetes experienced a significant decrease in HbA1c, insulin levels, and HOMA indices after taking 250 mg of oral elemental magnesium daily for 3 months.¹⁶ A meta-analysis conducted by Qu et al. in 2022 also found that oral magnesium replacement improved fasting blood glucose, insulin levels, and oxidative stress markers in patients with gestational diabetes compared to control groups.¹⁷ A meta-analysis conducted by Zhang et al. in 2016 observed a mean decrease of 2 mmHg in systolic blood pressure and a mean decrease of 1.78 mmHg in diastolic blood pressure with 368 mg/day magnesium supplementation for a median of 3 months in 2028 hypertension patients.¹⁸ Magnesium is believed to act as a natural calcium channel blocker, causing vasodilation, and may reduce oxidative stress, thus protecting against cardiovascular diseases.¹⁹ Our study found that the rates of

use of magnesium supplements for the regulation of blood glucose and hypertension were 5.9% and 10.9%, respectively. While routine magnesium use in patients with diabetes and hypertension may not yet be recommended, it's essential to keep in mind that these patient groups, which are frequently encountered in the clinic, may benefit from magnesium supplementation.

Our study has some limitations. Firstly, the number of participants was small. Additionally, the questionnaire was completed on an online platform which might have affected the quality of the responses. However, one of the positive aspects of our study was that we not only investigated the use of magnesium treatment and supplementation but also explored the specific magnesium preparations that internal medicine and family physicians preferred to prescribe.

Conclusion

Our study found that physicians who had more experience and were specialists were more interested in magnesium preparations. We also observed that the physicians preferred magnesium forms that were covered by the government's health insurance reimbursement for their patients. However, they preferred forms that had higher bioavailability for their own use. Furthermore, we found that family physicians provided more magnesium-rich dietary recommendations to their patients and prescribed magnesium supplements more frequently compared to internal medicine physicians. According to our results, training intervention studies could be planned for each group and residency training programs could be restructured about supplements like magnesium.

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Conflict of interest: No conflict of interest is declared by the authors

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