Clinical Research

Could Magnesium Be Associated with Urinary Incontinence and Overactive Bladder Disease in the General Population?

Ali Haydar YILMAZ[1,a], Faik ÖZEL[2]

[1]*Bilecik Şeyh Edebali University Faculty of Medicine Training and Research Hospital, Urology Clinic, Bilecik, Turkey*
[2]*Bilecik Şeyh Edebali University Faculty of Medicine Training and Research Hospital, Internal Medicine Clinic, Bilecik, Turkey*

ABSTRACT

Objective: Calcium (Ca) has been very well known to play a significant role in bladder detrusor contraction and stimulation. Magnesium (Mg), on the other hand, functions as an antagonist of Ca in the detrusor muscle. We designed our research on the question of whether magnesium may be associated with urological diseases such as overactive bladder and urinary incontinence.
Material and Method: A total of 124 patients with urinary incontinence and overactive bladder symptoms were randomized. One hundred twenty-two patients for control group who applied to the urology outpatient clinic and internal medicine outpatient clinic of the patients were included in the study. The effective parameters in Mg and bone metabolism, and those that may influence Mg metabolism were measured among the participating patients.
Results: Albumin values were statistically significant when compared with the control group ($p < 0.0001$, AUC =0.73). Likewise, ca values were found to be significant between the patient group and the control group according to the ROC analysis ($p = 0.0016$, AUC =0.61). Statistical significance was determined according to ROC analysis for phosphorus and parathormone and vitamin D (P value and AUC respectively $p < 0.0001$, AUC=0.65 and $p < 0.0001$, AUC =0.86, $p = 0.0007$, AUC =0.62).
Conclusion: According our cross sectional study magnesium level not statistically significiant. Since urinary incontinence and overactive bladder disease require chronic drug use, treatments provide symptomatic relief but do not cure. We believe that studies with more substantial patient participation are required to develop curative treatment and to fully understand the pathophysiology of these diseases.

Keywords: *Bladder, Magnesium, Overactive Bladder, Urinary incontinence, Vitamin D.*

ÖZ

Magnezyum Genel Popülasyonda İdrar Kaçırma ve Aşırı Aktif Mesane Hastalığı ile İlişkili Olabilir mi?

Amaç: Üriner inkontinans ve aşırı aktif mesane semptomları olan toplam 124 hasta randomize edildi. Kontrol grubu olarak üroloji polikliniğine ve hastaların dahiliye polikliniğine başvuran 122 hasta çalışmaya dahil edildi. Mg ve kemik metabolizmasındaki etkili parametreler ve Mg metabolizmasını etkileyebilecek parametreler, katılan hastalar arasında tetkik olarak alındı.
Gereç ve Yöntem: Üriner inkontinans ve aşırı aktif mesane semptomları olan toplam 124 hasta randomize edildi. Kontrol grubu olarak üroloji polikliniğine ve hastaların dahiliye polikliniğine başvuran 122 hasta çalışmaya dahil edildi. Mg ve kemik metabolizmasındaki etkili parametreler ve Mg metabolizmasını etkileyebilecek parametreler, katılan hastalar arasında tetkik olarak alındı.
Bulgular: Albümin değerleri kontrol grubu ile karşılaştırıldığında istatistiksel olarak anlamlıydı ($p < 0.0001$, AUC =0.73). Aynı şekilde ROC analizine göre hasta grubu ile kontrol grubu arasında ca değerleri anlamlı bulundu ($p = 0.0016$, AUC=0.61). Fosfor ve parathormon ve D vit için istatistiksel anlamlılık ROC analizine göre belirlendi (sırasıyla p değeri ve AUC, $p < 0.0001$, AUC =0.65 ve $p < 0.0001$, AUC =0.86, $p = 0.0007$, AUC =0.62).
Sonuç: Kesitsel çalışmamıza göre magnezyum düzeyi istatistiksel olarak anlamlı değildir. Üriner inkontinans ve aşırı aktif mesane hastalığı kronik ilaç kullanımını gerektirdiğinden tedaviler semptomatik rahatlama sağlamakta ancak tedavi etmemektedir. Küratif tedavinin bulunabilmesi ve bu hastalıkların patofizyolojisinin tam olarak aydınlatmak için daha fazla hasta katılımının olduğu çalışmaların gerekli olduğuna inanmaktayız.

Anahtar Sözcükler: *Mesane, Magnezyum, Aşırı Aktif Mesane, Üriner İnkontinans, Vitamin D.*

Bu makale atıfta nasıl kullanılır: Yılmaz AH, Özel F. Magnezyum Genel Popülasyonda İdrar Kaçırma ve Aşırı Aktif Mesane Hastalığı ile İlişkili Olabilir mi?. Fırat Tıp Dergisi 2023; 28(3): 226-230.

How to cite this article: Yilmaz AH, Ozel F. Could Magnesium Be Associated with Urinary Incontinence and Overactive Bladder Disease in the General Population?. Firat Med J 2023; 28(3): 226-230.

ORCID IDs: A.H.Y. 0000-0001-5797-0655, F.Ö. 0000-0002-2429-5355.

The difficulties encountered in treating frequency, urgency, urge incontinence, and nocturia caused by detrusor overactivity and sensory urgency disturb clinicians and patients (1). Recently, calcium (Ca) has been very well known to play a significant role in bladder detrusor contraction and stimulation. However, this contraction may have been more when the amount of intracellular Ca was high. Magnesium (Mg), on the other hand, functions as an antagonist of Ca in the detrusor muscle (2, 3).

In vitro studies have shown that the over active detrusor muscle contracts more than the typical detrusor muscle.

[a]Yazışma Adresi: Ali Haydar YILMAZ, Bilecik Şeyh Edebali University Faculty of Medicine Training and Research Hospital, Urology Clinic, Bilecik, Turkey
Tel: 0532 685 4943 e-mail: alicerrahcom@yahoo.com
Geliş Tarihi/Received: 23.01.2023 Kabul Tarihi/Accepted: 09.06.2023

These contractions are not nerve-mediated. However, increased alpha-adrenergic activity has been demonstrated to cause detrusor contraction in other studies (4, 5).

Recently, the data acquired from the detailed experimental and epidemiological studies through researches have suggested that Mg deficiency plays a significant role in several diseases. However, the exact pharmacological role of Mg in the pathological process in clinical medicine and how that contributes to diseases has not been fully clarified.

Using international forms, we aimed to define a metabolic relationship between all types of incontinence and overactive bladder disease in the current study. We designed our research on the question of whether it may be associated with significant urological diseases such as overactive bladder and urinary incontinence.

MATERIAL AND METHOD

The research was designed as a randomized controlled cross sectional prospective study. After receiving approval from the Bilecik Şeyh Edebali University Medical Faculty ethics committee (Approvel number E-10333602-050.04.01-147518), a total of 124 patients with urinary incontinence and overactive bladder symptoms who applied to the urology outpatient clinic and internal medicine outpatient clinic of the patients were included in the study. One hundred twentytwo partipiciants were randomly selected from the non-incontinence patients who applied to the outpatient clinic as the control group. Informed consent was obtained all participiants. Patients were evaluated as 3 groups according to incontinence types. Urge, stress, mix incontinence. Both men and women were among the patients who took part in the research. International ICIQ-SF (Urinary Incontinence Questionnaire Short Form) and OAB v8 (Over Active Bladder Short Questionnaire Form) forms validated in Turkish were filled in by the patients. The patients were included in the study regardless of any age and gender. All of the incontinence types were included in the study. The effective parameters in Mg and bone metabolism, and those that may influence Mg metabolism such as parathormone, Ca, phosphorus (P), albumin urea, and creatine D vit, were measured among the participating patients. The data on the patients were obtained from hospital records. Accordingly, the patients with the following diseases, which would cause Mg deficiency, were excluded from the study; patients with gastrointestinal disease or chronic bone diseases, patients who had Alzheimer, Dementia, and incontinence surgery operations or had acute urinary tract infection, patients with neurogenic bladder, chronic kidney failure, and chronic liver disease, and patients with painful bladder syndrome.

Magnesium analysis

The spectrophotometric method (xylidyl blue) was used for the determination of Mg in a Beckman Coulter AU2700. The reference values of the normal range of Mg were Male 1.8-2.6 mg/dl., Female 1.9-2.5 mg/dl. Other elements referance values of the normal ranges; D vit 6.6-49.9 ng/ml, albumin 4-5.5 gr/dl, üre 17-43 mg/dl, creatine 0.7-1.3 mg/dl, Ca 8.8-10.6 mg/dl, parathormone 15-68.3 ng/L, phosphorus 2.5-4.5 mg/dl.

Statistical analysis

The two-tailed independent samples t-test, one-way ANOVA with Tukey's multiple comparison test (95% confidence level), and Receiver Operating Characteristic (ROC) analyses were conducted in GraphPad 8.1 software. The median with minimum and maximum values was used in statistics. $p < 0.05$ was donated as statistically significant. ROC analysis was conducted to select a threshold value for distinguishing between normal and abnormal concentrations of different blood parameters. A graph depicting the tradeoff between sensitivity and specificity was generated as a ROC curve to aid decision-making. Sensitivity refers to the proportion of individuals with the disease correctly identified as positive by the test, while specificity represents the proportion of individuals without the disease correctly identified as negative. The mean area under the curve (AUC), along with its standard error (SE) at a 95% confidence level, was calculated to assess the overall discriminative ability of the test in differentiating between patients and healthy individuals. The area under the curve (AUC) values larger than 0.5 were evaluated in the ROC analysis.

RESULTS

Of the 124 patients, 28 (22.6%) were male and 96 (77.4%) were female in total. Median (Min-Max) ages of the patients were 70 (19-89). Median (Min-Max) age of of control group was 80 (10-90). Age distribution between groups was not statistically significant ($p = 0.138$) (Table 1, figure 1).

Table1. *Median (Min-Max) Age.*

	AGE	
	Control	Incontinence
Significance level	Median (Min-Max)	
	80 (10-90)	70 (19-89)

p =0.138.

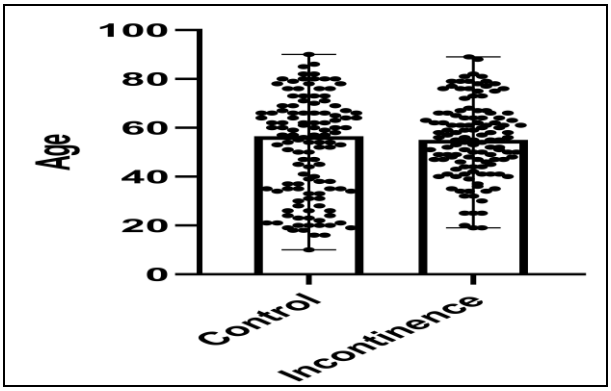

Figure 1. *Age bar diagram.*

According to incontinence types, stress (first group I) was distributed as 23 (18.5%) 6/17 M/F. While urge incontinence (second group II) was recorded as 58 (46.8%) 18/40 M/F, mixed incontinence (third group III) was defined as 43 (37.4%) 4/39 M/F (as shown table 2).

Table 2. *Types of incontinence in patients.*

	Mix Incontinence	Urge Incontinence	Stress Incontinence	Total
Male	4	18	6	28(%22.6)
Female	39	40	17	96(%77.4)
Total	43(%37.4)	58(%46.8)	23(%18.5)	

While no statistically significance was found between incontinence types according to OAB V8, there was a significant difference between I- III and II -III according to ICIQ-SF (respectively p =0.012, p =0.011) (Table 3, 4 and figure 2).

Table 3. *OAB V8 Median (Min-Max) distributions.*

	OAB-V8		
	I	**II**	**III**
	Median (Min-Max)		
	20 (9-29)	28 (6-34)	25 (10-35)
Tukey's multiple comparisons test	Significant?	Summary	Significance level
I vs. II	No	ns	p =0.906
I vs. III	No	ns	p =0.471
II vs. III	No	ns	p =0.111

NS: Not significant, I: Stress incontinence, II: Urge incontinence, III: Mix incontinence.

Table 4. *ICIQ-SF Median(Min-Max) distributions.*

	ICIQ-SF		
	I	**II**	**III**
	Median (Min-Max)		
	17 (3-20)	16 (3-19)	14 (5-19)
Tukey's multiple comparisons test	Significant?	Summary	Significance level
I vs. II	No	ns	p =0.800
I vs. III	Yes	*	p =0.012
II vs. III	Yes	*	p =0.011

*NS: Not significant, * Statistically significant, I: Stres incontinence, II: Urge incontinence, III: Mix incontinence.*

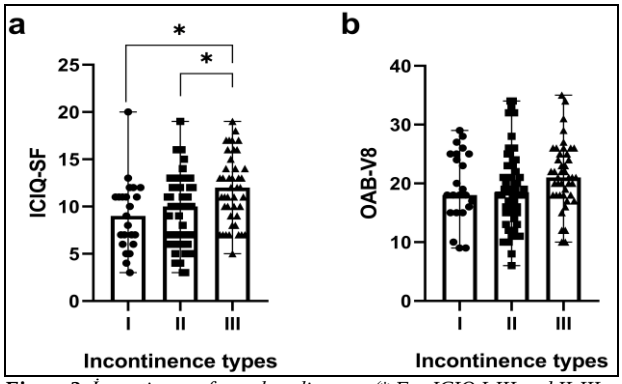

Figure 2. *İncontinance forms bar diagram (* For ICIQ I-III and II-III statistically significiant).*

When we assessed the electrolytes, according to ROC analysis, albumin values were statistically significant when compared with the control group (p <0.0001, AUC =0.73) (Figure 3).

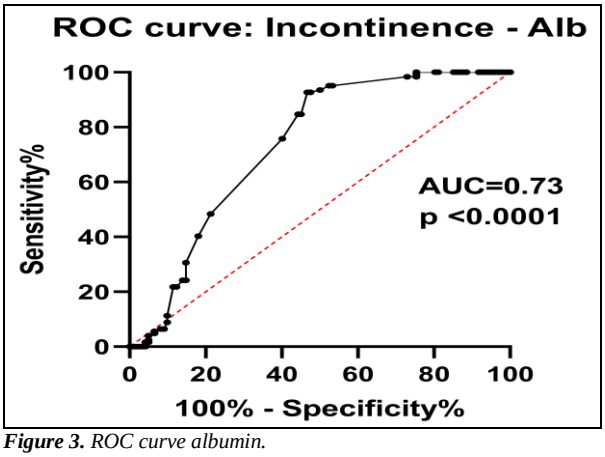

Figure 3. *ROC curve albumin.*

Likewise, Ca values were found to be significant between the patient group and the control group according to the ROC analysis (p =0.0016, AUC =0.61) (Figure 4).

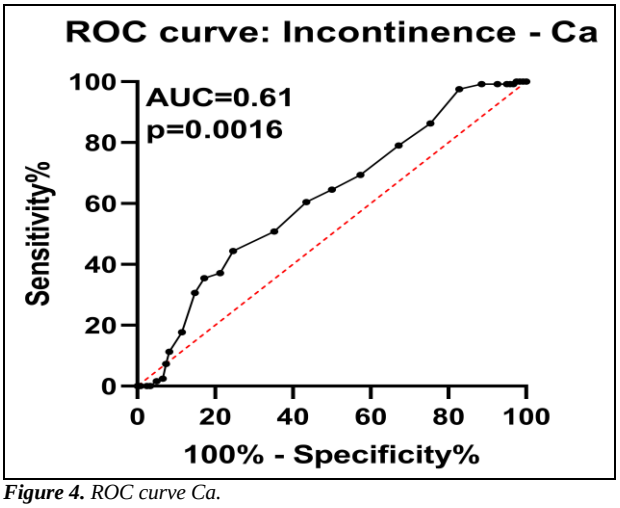

Figure 4. *ROC curve Ca.*

Statistical significance was determined according to ROC analysis for phosphorus and parathormone (p value and AUC respectively p <0.0001, AUC =0.65 and p <0.0001, AUC =0.86) (Figure 5, 6).

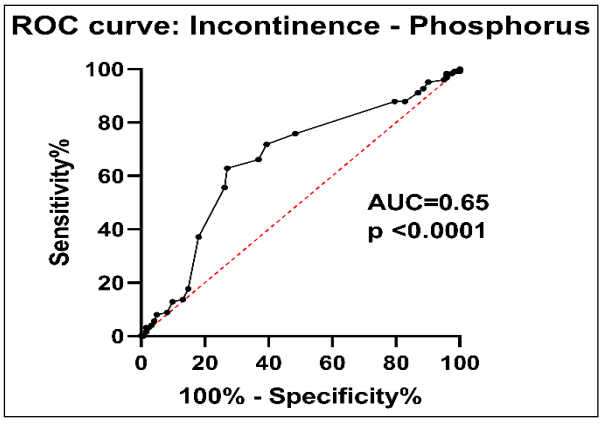

Figure 5. *ROC curve phosphorus.*

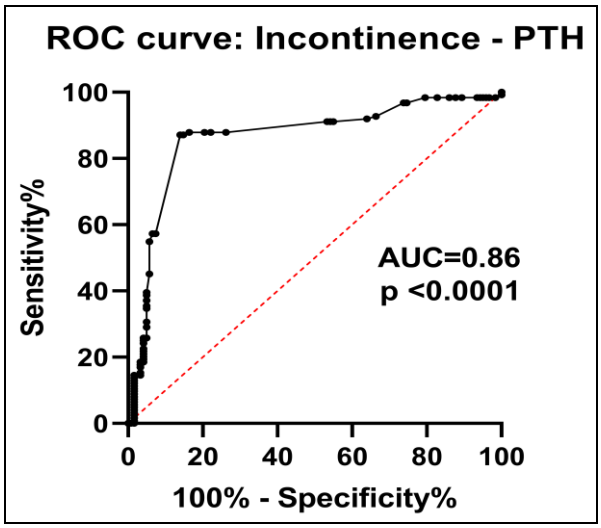

Figure 6. *ROC curve PTH (parathormone).*

Significance was also found for vitamin D (p =0.0007, AUC =0.62) (Figure 7).

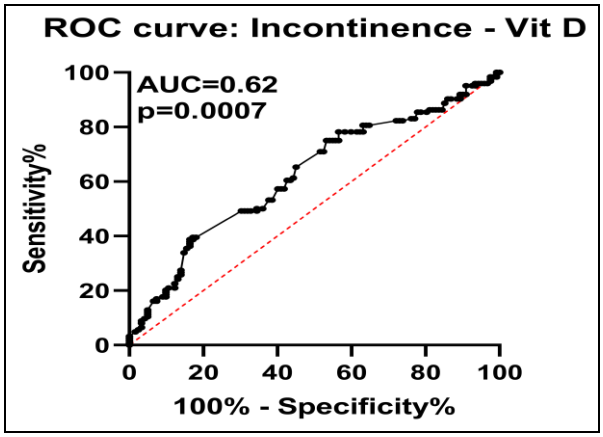

Figure 7. *ROC curve Vit D.*

No statistically significant difference was found between the magnesium and other electrolytes and the patient and control groups. We performed power analysis. We determined that sample size was sufficient for PTH and Ca, albumin, and phosphorus.

DISCUSSION

Urinary incontinence and overactive bladder disease, both of which have a detrimental impact on an individual's quality of life are significant health issues that affect a considerable portion of society, particularly the elderly. For centuries, people have been attempting to remedy this disease symptomatically, and researches into the origin of the disease are still ongoing (6).

Gordon et al. (7) reported a potentially positive impact of Mg treatment on frequency, urgency and nocturia. According the study magnesium hydroxide therapy was very well tolerated. However, the number of patients in that study was lower than ours, and they had included only female patients and patients in specific age groups. Mg prolongs muscle relaxation and prevents muscle spasms (8). According to in vitro studies, Mg was determined to suppress calcium ion flow across human detrusor membranes and reduce electrically induced and spontaneous muscle contractions (2). Due to these characteristics, it was included in our study, considering that it may affect overactive bladder and incontinence.

An amount equivalent to one-third of the daily Mg intake is excreted through the kidney (9). Mg homeostasis is regulated primarily in the nephron of the kidney (10). Mg excretion is raised by the kidneys in response to increasing food consumption or excessive Mg administration. In kidney failure, the fractional excretion of Mg increases gradually to maintain normal serum Mg levels until the late-stage hypomagnesemia occurs (11). In other words, the kidneys play a critical role in the regulation of Mg. Accordingly, we assessed kidney functions that could change the Mg balance in this study to ensure that it was optimized. The principal source of body Mg is bone. Whenever serum Mg levels are low, Mg is released rapidly from the surface of the bones (12). On the contrary, when serum Mg levels are high, the high level of Mg is bonded to the bone surface. Therefore, the D vit and phosphorus as hormones, Ca and parathormone, and also albumin to detect corrected Ca was evaluated among the patients to determine the vitamins and minerals, which may affect Mg metabolism and are essential in bone metabolism.

It was reported that low serum Mg levels were associated with inflammation (13). On the other hand, having high level of Mg was also associated with muscle weakness (14). From this perspective, a study like this was designed based on the hypothesis that 'may Mg deficit or excess be effective on the pelvic floor muscles, which are extremely effective in the mechanism of incontinence?'

According our evaluation magnesium levels not statically significiant, because since magnesium deficiency is not very common, no deficiency was found in our cross-sectional study, which was consistent with the general population.

Human bladder contraction mainly depends on Ca influx via L-type voltage-gated Ca channels which is upregulated in overactive bladder. According our results via ROC analysis, Ca levels statistically significant so consistency with literature. At the same time, parathormone levels related to ca regulation were also significant according to our analysis.

Vit D receptors have been found bladder detrusor muscle (15). According to our ROC analysis, Vit D was statistically significant compared to the control group. Consistent with this result, involuntary bladder contractions are often attributed to an increased signaling of RhoA/ROCK pathway (16). Vit D receptor agonist able to inhibit RhoA/ROCK signaling bladder strips and human bladder cells (17).

In a study carried out by Almasganj et al. (18) 30 patients with urge incontinence were given Mg hydroxide and concluded that the Mg group was more successful than the control group. In our opinion, the

patient group in this study was insufficient. In addition, this study only addressed urge urinary incontinence. However, our study evaluated all types of incontinence. **Conclusion:** Although according our cross sectional study magnesium level not statistically significant. we sought an answer to the question of whether all of these disorders could be linked to Mg, a mineral whose value has yet to be fully appreciated. Since urinary incontinence and overactive bladder disease require chronic drug use, treatments provide symptomatic relief but do not cure. We believe that studies with more substantial patient participation are required to develop curative treatment and to fully understand the pathophysiology of these diseases.

Declaration of conflicting interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Statement of ethics: Bilecik Şeyh Edebali University Medical Faculty ethics committee (Approvel number E-10333602-050.04.01-147518).

Informed consent: Informed consent was obtained all participants.

REFERENCES

1. Wall LL Diagnosis and management of urinary incontinence due to detrusor instability. Obstet Gynecol Sur 1990; 45: 1-36.
2. Montgomery BSI, Thomas PJ, Fry CH. The actions of extracellular Mg on isolated human detrusor muscle function. British J Urology 1992; 70: 262-8.
3. Akyüz O, Ardahanlı I, Aslan R. Relationshıp between chronic complications of type 2 diabetes mellitus and hypomagnesemia. J. Elem 2020; 2: 565-579.
4. Sibley GNA A comparison of spontaneous and nerve mediated activity in bladder muscle from man, pig and rabbit. J Physiology 1984; 354: 431-43.
5. Gözlersüzer Ö, Yalvaç B, Çakıroğlu B. Investigation of the effectiveness of magnetic field therapy in women with urinary incontinence: Literature review. Urologia 2023; 90: 51-7.
6. Leron E, Weintraub AY, Mastrolia SA, Schwarzman P. Overactive Bladder Syndrome: Evaluation and Management. Curr Urol 2018; 11: 117-25.
7. Gordon D, Groutz A, Ascher-Landsberg J, Lessing JB, David MP, Razz O. Double-blind, placebo-controlled study of Mg hydroxide for treatment of sensory urgency and detrusor instability. Br J Obstet Gynaecol 1998; 105: 667-9.
8. Kocot J. Mg in medicine and treatment. J Elem 2014;19: 1179-92.
9. Aikawa JK. Mg: its biological significance. CRC Press. inc. Boca Raton, Florida; 1981.
10. Cole DEC, Quamme GA. Inherited disorders of renal Mg handling. J Am Soc Nephrol 2000; 11: 1937-47.
11. Sutton RAL, Domrongkitchaiborn S. Abnormal renal Mg handling. Miner Electrolyte Metab 1993; 19: 232-40.
12. Martini LA. Mg supplementation and bone turnover. Nutr Rev 1999; 57: 227-9.
13. Brugère CM, Nowacki W, Daveau M, Gueux E, Linard C, Rock E, Lebreton J, Mazur A, Rayssiguier Y. Inflammatory response following acute Mg deficiency in the rat. Biochim Biophys Acta 2000; 1501: 91-8.
14. Rude RK, Singer FR. Mg deficiency and excess. Annu Rev Med 1981; 32: 245-59.
15. Morelli A, Squecco R, Failli P et al. The vitamin D receptor agonist elocalcitol upregulates L-type calcium channel activity in human and rat bladder Am J Physiol Cell Physiol 2008; 294: C1206-14.
16. Hegde SS. Muscarinic receptors in the bladder: from basic research to therapeutics. Br J Pharmacol 2006; 147: S80-7.
17. Morelli A, Vignozzi L, Filippi S et al. BXL-628, a vitamin D receptor agonist effective in benign prostatic hyperplasia treatment, prevents RhoA activation and inhibits RhoA/Rho kinase signaling in rat and human bladder. Prostate 2007; 67: 234-47.
18. Almasganj F, Saneifard F, Shokoohi H. The effects of mg hydroxide on urge incontinence. RJMS 2003;10: 177-81.