A Higher Ratio of Serum Calcium to Magnesium Is Associated With Aggressive Clinicopathological Characteristics in the Patients Who Underwent Radical Prostatectomy

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Purpose: Changes in magnesium (Mg) concentration and calcium-to-magnesium ratio (Ca/Mg) play a critical role in cancer cell proliferation. In this study, we evaluated the association between preoperative Ca/Mg ratio and clinicopathological characteristics of prostate cancer.

Materials and Methods: Preoperative serum levels of Ca and Mg, as well as the Ca/Mg ratio, were retrospectively analyzed in 319 consecutive patients with prostate cancer who underwent radical prostatectomy at our institution between February 2014 and June 2016. Blood Ca and Mg levels, together with the Ca/Mg ratio, were analyzed in relation to the patients' demographic and clinicopathological characteristics.

Results: Preoperative Ca/Mg ratio was significantly higher in patients with pathologic Gleason score (pGS) ≥ 8 than in those with pGS ≤ 7 (mean [95% confidence interval]: 4.45 [4.35–4.56] vs. 4.32 [4.27–4.38], $p=0.037$). The Ca/Mg ratio was positively correlated with preoperative prostate-specific antigen (PSA) levels ($r=0.116$, $p=0.039$) and PSA density ($r=0.156$, $p=0.005$). Ca/Mg ratio was a preoperative predictor of high pGS (≥ 8) according to multiple logistic regression analysis (odds ratio, 1.752; 95% confidence interval, 1.002–3.064; $p=0.049$).

Conclusions: A high serum Ca/Mg ratio was closely associated with worse clinicopathological parameters (high PSA and PSA density and pGS ≥ 8), suggesting that the Ca/Mg ratio may be a useful serological marker for further characterization of oncologic features in prostate cancer. A multicenter prospective study with long-term follow-up is recommended to further assess the utility of this cost-effective marker as a prognostic indicator of prostate cancer. (Korean J Urol Oncol 2018;16:25-31)

Key Words: Calcium • Magnesium • Prostatic neoplasms

INTRODUCTION

In Korea, prostate cancer (PCa) is the most common malignancy of the genitourinary tract and the fifth most common type of cancer among men.¹ Approximately 11,062 new PCa cases and 1,862 PCa-related deaths occurred in Korea in 2016,² and PCa had an age-adjusted mortality rate of 28.0 deaths per 100,000 cases.³ Several aspects, including environmental factors, changes in dietary habits, medical advances in laboratory

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diagnosis, and campaigns for prostate-specific antigen (PSA) screening, are associated with the increased incidence of PCa.^{4,5} In the United States, PCa is the most prevalent cancer among men and the second leading cause of cancer-related mortality.⁶ Contemporary guidelines recommend that treatment decisions should be based on tumor features, baseline PSA levels, patient age, comorbidity, life expectancy, and quality of life.⁷

Calcium (Ca)-magnesium (Mg) imbalance is implicated in PCa.⁸ Two recent studies found that high serum Ca levels are associated with aggressive lesions or fatal PCa.^{9,10} Furthermore, Dai et al.¹¹ showed that low blood Mg levels and a high Ca/Mg ratio were significantly associated with high-grade PCa (Gleason score ≥ 7). In Western countries, intake of dietary Mg is often lower than the recommended amount of 6 mg/kg/day.¹² The 1999–2000 National Health and Nutrition Examination Survey found that 79% of American adults have an Mg intake below the Recommended Dietary Allowance.¹³ In Korean adult men, over half of population showed intakes of magnesium less than the estimated average requirement.¹⁴ Inadequate calcium intake was common. According to the 2013 National Health and Nutrition Survey, calcium intake is only 70% of the recommendation. Especially in elderly people over 65 years old.¹⁵ However, a relationship between Ca/Mg ratio and PCa aggressiveness has not yet been established in Asian men. Therefore, we investigated the potential relationship of serum Ca levels, Mg levels, and Ca/Mg ratio with clinical variables, such as age, demographics, PSA levels, and clinicopathological parameters, in patients who underwent radical prostatectomy.

MATERIALS AND METHODS

We retrospectively reviewed prospectively maintained data of 319 patients who underwent radical prostatectomy between February 2014 and June 2016 and were histologically confirmed to have PCa. The Ethics Committee of Kyungpook National University Medical Center approved the study protocol (approval number: KNUMC 2017-03-036). The collection and analysis of all samples was approved by the Institutional Review Board of Kyungpook National University Medical Center. Age, body mass index, European Cooperative Oncology Group (ECOG) performance status (PS), drinking status, smoking status, hypertension, diabetes mellitus (DM), preoperative PSA levels, PSA density, biopsy findings, pathologic Gleason score (pGS), PCa stage (TNM classification), and blood levels

of Ca and Mg were obtained from the medical charts. Ca, Mg, and the Ca/Mg ratio were entered into the analysis as potential predictors and were assessed in relation to the patients' demographic and clinicopathological characteristics.

The *t*-test and analysis of variance test with *post hoc* analyses were used to compare the Ca levels, Mg levels, and Ca/Mg ratio on stratification according to various clinical parameters. Correlations between Ca/Mg ratio and clinicopathological variables, including age, PSA levels, and PSA density, were assessed. Multiple linear regression analysis was performed to evaluate independent variables that influence high pGS (≥ 8). Differences with $p < 0.05$ were considered statistically significant. IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA) was used for statistical analyses.

RESULTS

1. Baseline characteristics

The mean age, serum Ca levels, Mg levels, and Ca/Mg ratio were 66.25 ± 6.34 years, 9.43 ± 0.50 ng/mL, 2.18 ± 0.20 ng/mL, and 4.36 ± 0.46 , respectively. The mean body mass index was 24.08 ± 3.06 kg/m².

1) Mg levels, Ca levels, and Ca/Mg ratio according to demographics

On stratification of patients into four groups according to age (< 60 , 60–64, 65–69, and ≥ 70 years), we found that the Ca levels and Ca/Mg ratio were significantly lower, whereas Mg levels were higher in older patients than in younger patients. Mg levels were lower in patients with ECOG PS 1 than in those with ECOG status 0 ($p = 0.021$) and in patients with DM than in those without DM ($p < 0.001$). Meanwhile, the Ca/Mg ratio was higher in patients with DM than in those without DM ($p < 0.001$). No significant differences in Ca/Mg ratio were noted on stratification of patients according to body mass index, ECOG status, drinking status, smoking status, or history of hypertension (Table 1).

2) Mg levels, Ca levels, and the Ca/Mg ratio according to preoperative and postoperative clinicopathological factors

The Ca/Mg ratio was significantly higher in patients with PSA levels of > 20 ng/mL than in those with 0–4 ng/mL ($p = 0.043$) and in patients with pGS ≥ 8 than in those with pGS ≤ 7 (mean [95% confidence interval]: 4.45 [4.35–4.56] vs. 4.32

Table 1. Association between calcium (Ca), magnesium (Mg), and Ca/Mg ratio with study population demographics

Variable	No.	Ca		p-value	Mg		p-value	Ca/Mg		p-value
		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Age (yr)				0.099			0.059			0.004
< 60	49	9.57	9.43–9.71	0.044*	2.14	2.08–2.2	0.021 [†]	4.53	4.37–4.68	<0.001 [†]
60–64	58	9.47	9.37–9.56		2.19	2.13–2.24		4.37	4.25–4.48	
65–69	106	9.40	9.3–9.5	0.018 [†]	2.16	2.12–2.19	0.027 [†]	4.40	4.3–4.49	0.019 [†]
≥ 70	106	9.37	9.27–9.47		2.22	2.18–2.25		4.25	4.18–4.32	
BMI (kg/m ²)				0.241			0.256			0.589
< 23	101	9.36	9.27–9.45		2.17	2.13–2.2		4.36	4.27–4.45	
23–27.4	185	9.46	9.39–9.54		2.19	2.16–2.22		4.35	4.28–4.42	
≥ 27.5	33	9.45	9.26–9.64		2.14	2.08–2.19		4.44	4.31–4.57	
ECOG PS				0.369			0.021			0.216
0	165	9.45	9.38–9.53		2.20	2.17–2.24		4.33	4.25–4.41	
1	154	9.40	9.32–9.48		2.15	2.12–2.18		4.40	4.33–4.46	
Drinking				0.529		–	0.026		–	0.081
No	222	9.42	9.35–9.48		2.16	2.14–2.19		4.39	4.33–4.45	
Yes	97	9.46	9.35–9.56		2.22	2.18–2.25		4.29	4.21–4.38	
Smoking				0.610			0.568			0.395
No	191	9.42	9.36–9.48		2.19	2.16–2.21		4.33	4.28–4.39	
Current	49	9.49	9.33–9.66		2.18	2.1–2.26		4.42	4.24–4.59	
Quit	79	9.41	9.29–9.54		2.16	2.11–2.2		4.40	4.29–4.5	
Hypertension				0.147			0.616			0.112
No	178	9.39	9.32–9.47		2.18	2.16–2.21		4.33	4.27–4.38	
Yes	141	9.47	9.4–9.55		2.17	2.14–2.21		4.41	4.32–4.5	
Diabetes				0.869			<0.001			<0.001
No	270	9.43	9.37–9.49		2.20	2.18–2.23		4.31	4.26–4.36	
Yes	49	9.42	9.28–9.56		2.05	2–2.1		4.63	4.47–4.8	

CI: confidence interval, BMI: body mass index, ECOG PS: European Cooperative Oncology Group Performance Status.

* < 60 years vs. 65–69 years. [†] < 60 years vs. ≥ 70 years. [‡] 65–69 years vs. ≥ 70 years.

[4.27–4.38], $p=0.037$). Finally, Ca levels differed significantly between patients with clinical stage $\leq T2$ and those with clinical stage $\geq T3$ ($p=0.020$), whereas Mg levels differed significantly between patients with pathologic stage N0/x and those with stage $\geq N1$ ($p=0.024$) (Table 2).

3) Correlations between Ca/Mg ratio and clinicopathological parameters

Blood Ca levels were significantly associated with PSA levels and PSA density. The Ca/Mg ratio was positively correlated with preoperative PSA levels ($r=0.116$, $p=0.039$) and PSA density ($r=0.156$, $p=0.005$) (Table 3).

4) Multivariate analysis of preoperative predictors of high Gleason score (≥ 8)

In multivariable modeling, preoperative PSA (odds ratio [OR], 1.026; 95% confidence interval [CI], 1.008–1.044,

$p=0.004$) and Ca/Mg (OR, 1.752; 95% CI, 1.002–3.064, $p=0.049$) were associated with high Gleason score (≥ 8) adjusted for age and BMI (Table 4).

DISCUSSION

In the present study, we investigated the potential of Ca, Mg, and Ca/Mg ratio as biomarkers for identifying high-grade PCa. Our analysis indicated that relatively high Ca levels and low Mg levels, albeit at subclinical limits, can predict more aggressive PCa. Moreover, the Ca/Mg ratio was positively correlated with preoperative PSA levels and PSA density.

The Ca/Mg ratio increases or decreases with cell proliferation or apoptosis, respectively.⁸ Among other metals, Ca and Mg concentrations are significantly higher in malignant prostate tumors than in benign prostate tumors.¹⁶ Additionally, intranuclear Ca levels have increased with aging and is believed to

Table 2. Relationship of preoperative and postoperative clinicopathological factors with calcium (Ca), magnesium (Mg), and Ca/Mg ratio

Variable	No.	Ca		p-value	Mg		p-value	Ca/Mg		p-value
		Mean	95% CI		Mean	95% CI		Mean	95% CI	
PSA (ng/mL)				0.067			0.401			0.136
0-4	43	9.26	9.17-9.36	0.009*	2.18	2.13-2.24	0.090 [†]	4.27	4.16-4.38	0.043 [‡]
4.1-10	165	9.48	9.41-9.56		2.18	2.15-2.21		4.38	4.31-4.46	
10.1-20	71	9.40	9.28-9.52		2.20	2.14-2.25		4.31	4.21-4.4	
>20	40	9.44	9.24-9.64		2.13	2.06-2.2		4.47	4.29-4.65	
Biopsy GS			-	0.287		-	0.305		-	0.056
≤7	228	9.41	9.35-9.47		2.19	2.16-2.21		4.33	4.28-4.39	
≥8	91	9.48	9.36-9.6		2.16	2.11-2.21		4.44	4.33-4.55	
Clinical T stage			-	0.020		-	0.630		-	0.122
≤T2	279	9.41	9.35-9.46		2.18	2.16-2.2		4.35	4.29-4.4	
≥T3	40	9.6	9.41-9.79		2.16	2.09-2.24		4.47	4.33-4.6	
Pathologic GS			-	0.416		-	0.070		-	0.037
≤7	226	9.41	9.35-9.47		2.19	2.17-2.22		4.32	4.27-4.38	
≥8	93	9.47	9.35-9.59		2.15	2.1-2.19		4.45	4.35-4.56	
Pathologic T stage			-	0.623		-	0.495		-	0.284
≤T2	174	9.42	9.35-9.49		2.19	2.16-2.21		4.34	4.28-4.4	
≥T3	145	9.44	9.36-9.53		2.17	2.14-2.21		4.40	4.31-4.48	
Pathologic N stage			-	0.076		-	0.024		-	0.209
N0/Nx	302	9.44	9.39-9.5		2.18	2.16-2.21		4.36	4.31-4.41	
N1	14	9.20	8.9-9.5		2.06	1.91-2.2		4.52	4.24-4.79	
Margin status			-	0.390		-	0.984		-	0.843
Negative	109	9.46	9.37-9.55		2.18	2.14-2.21		4.37	4.3-4.44	
Positive	210	9.41	9.34-9.48		2.18	2.15-2.21		4.36	4.29-4.43	

CI: confidence interval, PSA: prostate-specific antigen, GS: Gleason score.

*0-4 ng/mL vs. 4.1-10 ng/mL. [†]10.1-20 ng/mL vs. >20 ng/mL. [‡]0-4 ng/mL vs. >20 ng/mL.**Table 3.** Correlations between calcium (Ca), magnesium (Mg), and Ca/Mg ratio with continuous variables

Variable	Ca		Mg		Ca/Mg ratio	
	r	p-value	r	p-value	r	p-value
Age	-0.155	0.005	0.119	0.033	-0.197	<0.001
Preoperative PSA	0.114	0.041	-0.053	0.349	0.116	0.039
PSA density	0.133	0.018	-0.077	0.168	0.156	0.005

PSA: prostate-specific antigen, r: correlation coefficient.

Table 4. Multivariate analysis of preoperative predictors of high Gleason score (≥8) according to the multivariate logistic regression analysis

Variable	OR	95% CI	p-value
Age	1.015	0.974-1.057	0.477
BMI	1.036	0.953-1.127	0.403
Preoperative PSA	1.026	1.008-1.044	0.004
Ca/Mg ratio	1.752	1.002-3.064	0.049

OR: odds ratio, CI: confidence interval, BMI: body mass index, PSA: prostate-specific antigen, Ca: calcium, Mg: magnesium.

have pathologic significance in prostate growth disorders.¹⁷ High dietary Ca intake is positively associated with increased risk of PCa.^{18,19} In their prospective, cohort study, Skinner and Schwartz¹⁰ reported an approximately 3-fold increase in the risk for fatal PCa among men whose serum Ca levels are in the upper tertile of the distribution of values for the general population. While such an association had not been previously demonstrated in Korean patients, our present study found that blood Ca levels were significantly associated with PSA levels and density. Moreover, Ca levels differed significantly with

clinical T stage ($\leq T2$ vs. $\geq T3$).

Mg is essential for many biological processes, including the synthesis of organic molecules, cell proliferation, energy production, muscle contraction and relaxation, bone development, mineral metabolism, and glucose homeostasis.²⁰ In North America, Mg intake falls short of dietary recommendations for a large segment of the population.²¹ Low Mg intake and/or serum Mg concentrations have been associated with a number of diseases and health conditions, including DM,²² breast cancer,²³ and colorectal cancer.²⁴ In agreement with previous studies, our study involving a PCa cohort found that Mg levels were significantly lower in patients with DM than in those without DM. Furthermore, a population-based prospective study revealed that high Mg intake may reduce the occurrence of colorectal cancer in women.²⁴ Yang et al.²⁵ believed that Mg intake from drinking water and other dietary sources may significantly reduce the risk of PCa development. Dai et al.¹¹ showed that low blood Mg levels and a high Ca/Mg ratio were significantly associated with high-grade PCa ($pGS \geq 7$). In agreement with these previous observations, we found that the Ca/Mg ratio was significantly higher in patients with $pGS \geq 8$ than in those with $pGS \leq 7$. Furthermore, Mg levels differed significantly with pathologic N stage ($N0/x$ vs. $\geq N1$). Mg can prevent carcinogenesis through at least 2 biologically possible mechanism, namely that intracellular Mg may enhance the fidelity of DNA replication or prevent changes that trigger the carcinogenic process.²⁶ Also, Mg levels differed significantly with ECOG PS (0 vs. 1). Patients with poor ECOG PS are less likely to have dietary intake and lack of essential elements. In addition, malignancy can influence metabolic and physiological changes that affect the patient's nutritional status and required nutrients.²⁷ Lower Mg concentrations affect the carcinogenic pathways of the body, as noted above. As a result, poorer ECOG PS is considered to be a phenotype of disease progression.

In this study, Ca and Mg individually showed significant differences in several pathologic characteristics, but did not show a consistent association. The Ca/Mg ratio is believed to be more related to aggressiveness of PCa than to Ca or Mg alone. The TRPM7 is regulated by serum Mg concentrations, which is a magnesium-nucleotide-regulated metal current channel. It is expressed in both PCa and control cells, but is more expressed in PCa cells. The increase of cell proliferation was significantly higher in high Ca/Mg group than in control group.⁸ According to this result, it can be assumed that Ca/Mg ratio is related to

the aggressiveness of the PCa. In addition, Ca/Mg ratio was positively correlated with PSA and PSAD.

Choosing an appropriate treatment strategy for PCa primarily depends on the preoperative risk of disease progression. Patients will be offered different treatment options based on the outcomes of risk evaluation.²⁸ In counseling, physicians rely mostly on pGS, which is currently the most reliable prognostic marker in PCa. PSA levels and density are also useful biological markers for the management of patients with PCa.²⁹ A recent study reported the superiority of PSA density over PSA levels for prediction of upgrading among patients with $pGS=6$.³⁰ A possible explanation for the predictive superiority of PSA density over PSA levels may involve the effect of prostate size. Specifically, large prostates are more likely to have an enlarged transition zone, which is associated with low incidence of PCa. In this context, the Ca/Mg ratio is a useful serological marker for further characterization of oncologic features in patients with PCa.

To the best of our knowledge, the present study is the first to examine and observe a significant relationship between Ca/Mg ratio and the aggressiveness of PCa among patients underwent radical prostatectomy. The major strengths of our study include the prospectively maintained cohort and relatively large sample size (319 patients, albeit from a single center). Our study also has several potential limitations. First, the data were analyzed in a retrospective manner. Because the follow-up period was short, we did not perform survival analysis to analyze recurrence-free survival after surgery. Despite these limitations, our study clearly showed that a high preoperative Ca/Mg ratio was associated with a high risk of high-grade PCa, suggesting the interaction between Mg and Ca, which play a role in the pathogenesis and progression of PCa. These findings, if confirmed, may pave the way for individualized medical treatment or adjuvant care of patients with PCa.

CONCLUSION

We found that a high Ca/Mg ratio was closely associated with worse clinicopathological parameters, such as high PSA levels, high PSA density, and $pGS \geq 8$. Our results suggest that the Ca/Mg ratio may be a useful serological marker for further characterization of the oncologic features of patients with PCa. A multicenter prospective study with long-term follow-up is recommended to further assess the utility of this ubiquitous and

cost-effective marker as a prognostic indicator of PCa.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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