



APPETIZING EFFECT OF CALCIUM CARBONATE/MAGNESIUM CARBONATE COMBINATION CHEWABLE TABLETS COMPARED WITH CALCIUM CARBONATE TABLETS IN HEMODIALYSIS PATIENTS

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ABSTRACT:

Objectives: Protein Energy Malnutrition (PEM) are more predominant in hemodialysis patients. The presence of hypo-albuminemia is indicative for both malnutrition and mortality. The aim of this study is to evaluate the differences between the two phosphate binders in terms of Simplified Nutritional Appetite Questionnaire (SNAQ) score (4-20) value, albumin level (ALB), and blood urea nitrogen (BUN).

Methods: The randomized, controlled, open study was conducted at renal / hemodialysis unit of King Hussein Medical Hospital (KMH) for six weeks. Patients was randomly allocated into either interventional groups (Group I or II) or control groups (Group III or IV). Analysis was conducted by either Kruskal-Wallis Test followed by Mann-Whitney U-Test for SNAQ score (4-20) value or one-way ANOVA test followed by Tukey Kramer Post Hoc test for ALB and BUN.

Results: A total of 71 hemodialysis patients were finally included in this study. The mean age was 40.81 ± 2.31 years, and 37 males (52.11%) were male. SNAQ score (4-20) value was increased significantly in both Group I and II (+3 (4) and +4 (5), respectively). Highest SNAQ score (4-20) value was significantly between Group II and Group III (+4 (10)) or Group IV (+4 (5)).

Conclusion: In this study, we revealed that our interventional phosphate binder had a significant appetizing effect in HD patients especially when the acid suppressing agent is H₂-Blockers. This appetizing effect may improve the nutritional status and may have a positive impact on both quality of life and mortality of HD patients.

KEY WORDS: Hemodialysis, Phosphate binders, Appetizer, Malnutrition.

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INTRODUCTION

Low energy intake and Protein Energy Malnutrition (PEM) are more predominant in patients undergoing maintenance hemodialysis and may contribute to the high incidence of wasting and malnutrition due to the kidney's unique role in nutrients disposition and the malnutrition by itself will increase the morbidity and mortality among hemodialysis patients¹. Many factors are responsible for inadequate nutrient intakes in dialysis patients, among which anorexia and acid gastrointestinal disorders are more prevalent in dialysis patients². Those disorders may be of significant concern, because the symptoms with which they are associated can result in reduces oral energy and protein intakes, decrease quality of life, and development of malnutrition and cachexia. Anorexia may be primarily due to uremic toxin accumulation and may be due to other underlying illnesses such as diabetes mellitus with impaired gastric emptying³⁻⁹.

The presence of hypoalbuminemia and decreased levels of other markers that are indicative for malnutrition, especially prealbumin are potent

indicators for morbidity and mortality in patients with end stage renal diseases¹⁰. Treatment modifications that can help to prevent or treat malnutrition are adequate dialysis, addition of balance food supplements (restricting phosphorus intake from food, but because it is difficult to maintain and it can exacerbate protein malnutrition), and minimizing constipation that associated with calcium phosphate binders.

Methods

This randomized, controlled, open label study was conducted at renal /hemodialysis unit of King Hussein Medical Center (KHMC) for six weeks in order to evaluate the differences between the four hemodialysis (HD) patient's groups as fully described in Table 1 in terms of SNAQ score (4-20) value, ALB, and BUN. After the study was approved from the IRB committees at the Jordanian Royal Medical Services, patients who did meet the inclusion and didn't meet the exclusion criteria as described in Figure (1) were enrolled in this study.

Table 1: Hemodialysis participants group number and description.

Group #	Interventional Groups		Control Groups	
	Group I	Group II	Group III	Group IV
Description	HD participants who are taking PPIs + CaCO ₃ /MgCO ₃ combination chewable tablets.	HD participants who are taking H ₂ -Blockers + CaCO ₃ / MgCO ₃ combination chewable tablets.	HD participants who are taking PPIs + only CaCO ₃ tablets.	HD participants who are taking H ₂ -Blockers+ only CaCO ₃ tablets.
#: Number. HD: Hemodialysis. PPIs: Proton pump inhibitors. CaCO ₃ : Calcium carbonate. MgCO ₃ : Magnesium carbonate. H ₂ : Histamine.				

All possible required retrospective data of three months ago for the tested four groups were collected before the study period was started. After retrospective data were completed, the four studied groups were followed for 6 weeks in which the following outcomes were measured and assessed in the following basis:

- ALB and BUN level were measured on weekly basis for the first 2 weeks and then every other week in our KHMC chemistry laboratories.
- SNAQ Score (4-20) value were assessed on weekly basis.

Inclusion criteria

- Age ≥ 18 and < 60 years.
- Hemodialysis ≥ 3 months.
- Using CaCO_3 as phosphate binder ≥ 3 months.
- Using either H_2 -Blockers or PPIs ≥ 3 months

Exclusion criteria

- Serum cCa^{+2} level > 10.2 mg/dl.
- $\text{cCa}^{+2} \times \text{PO}_4^{-3} > 55$ mg^2/dl^2 .
- Serum $\text{Mg}^{+2} > 3.5$ mg/dl.
- Disorders leading to compliance issues.
- Positive history of dysphagia or swallowing disorders or bowel obstruction.

Figure 1. Inclusion and exclusion criteria for hemodialysis patients.

In the interventional prospective follow-up, the CaCO_3 tablets in both Group I and Group II were totally replaced by $\text{CaCO}_3/\text{MgCO}_3$ combination chewable tablets without a washout period (maximum 6 tablets per day) in which each 1 tablet of CaCO_3 1250 mg was replaced by 2 tablets of $\text{CaCO}_3/\text{MgCO}_3$ combination 680 mg/80 mg (Rennie[®]), while keeping all other medications without any change. During the follow-up phase, if serum Mg^{+2} level was ≥ 3.5 mg/dl and persisted for 1 week or serum Mg^{+2} level was ≥ 4.5 mg/dl we dropped-out the HD participant from our study. The CaCO_3 tablets in the Group III and Group IV were kept without any change in the prospective follow-up phase.

The collected data at the end of 6 weeks of each desired outcome in the different four studied groups were analyzed using either Kruskal-Wallis Test followed by Mann-Whitney U-Test with Bonferroni correction for SNAQ score (4-20) value or one-way ANOVA test followed by Tukey Kramer Post Hoc test for ALB and BUN (with p -value < 0.05 as a level of significance) to determine whether there were significant differences. For each studied group of the four studied groups, mean \pm SD was compared between before interval versus after interval for ALB and BUN by using paired T-Test while median (Range) between before interval versus after interval was compared for SNAQ score (4-20) by using Wilcoxon Signed Ranks Test. One-Way ANOVA test analysis was used to present the demographic characteristics of age (years), body surface area

(BSA) (m^2), body mass index (BMI) (kg/m^2), duration of dialysis (months), duration of using CaCO_3 tablets as phosphate binder (months), duration of using either PPIs or H_2 -Blockers (months) and HD duration per session (hours) by comparing the mean \pm SEM among groups. In case of gender (male or female) and HD frequency per week (%) data were presented as percentage of frequency.

RESULTS

The recruitment, randomization, and dropout processes of all 142 eligible HD participants and the medical and medication history of the study candidates in each group are summarized in Figure (2-4). All demographic characteristics of 71 HD participants in the four studied groups are summarized in Tables (2-3). All comparative results of the tested variables within and between four studied groups are summarized in Table (4-5). A total of 71 hemodialysis patients were finally included in this study. The mean age was 40.81 ± 2.31 years, and 37 males (52.11%) were male. SNAQ score (4-20) value was increased significantly in both Group I and Group II (+3 (4) vs +4 (5), respectively) after CaCO_3 tablets were totally replaced by $\text{CaCO}_3/\text{MgCO}_3$ combination chewable tablets. This SNAQ score (4-20) significant increasing was accompanied by a significant increasing in the levels of albumin ($+0.43 \pm 0.12$ vs $+0.56 \pm 0.11$, respectively) and BUN ($+12.03 \pm 5.75$ vs $+14.34 \pm 6.21$, respectively). When comparing between comparative four studied groups, the highest SNAQ score (4-20) value was

significantly between Group II and Group III (+4 (10)) or Group IV (+4 (5)) followed by Group I and Group III (+3 (8)) or Group IV (+3 (6)), and this SNAQ score (4-20) significantly increasing was also accompanied by a significant parallel increasing in

both serum albumin and BUN levels. In contrast, SNAQ score (4-20) value, serum albumin level, and BUN level were insignificantly changed between interventional groups (Group I vs Group II) and between control groups (Group III vs Group IV).

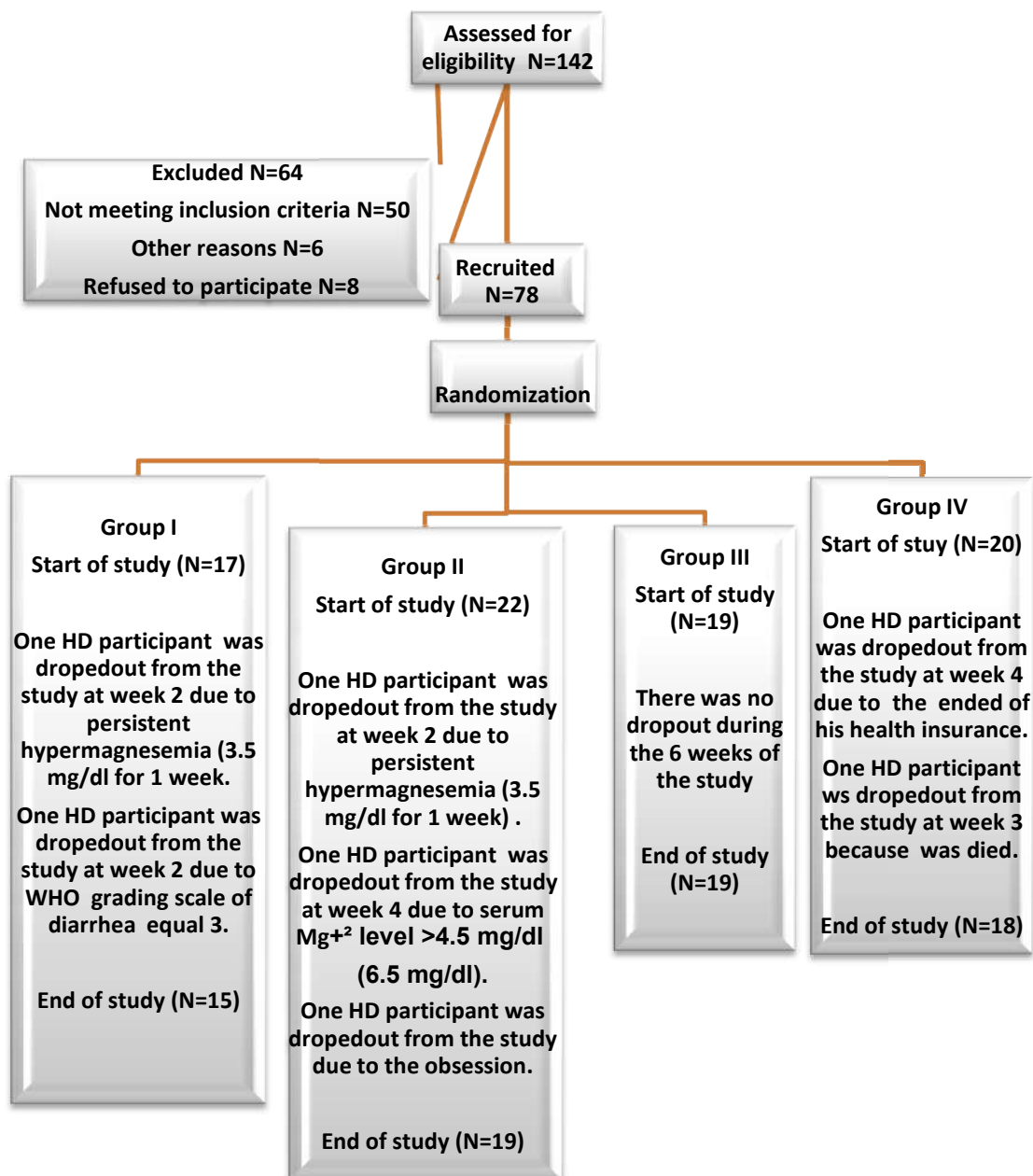


Figure 2: Recruitment, randomization, and dropout processes scheme.

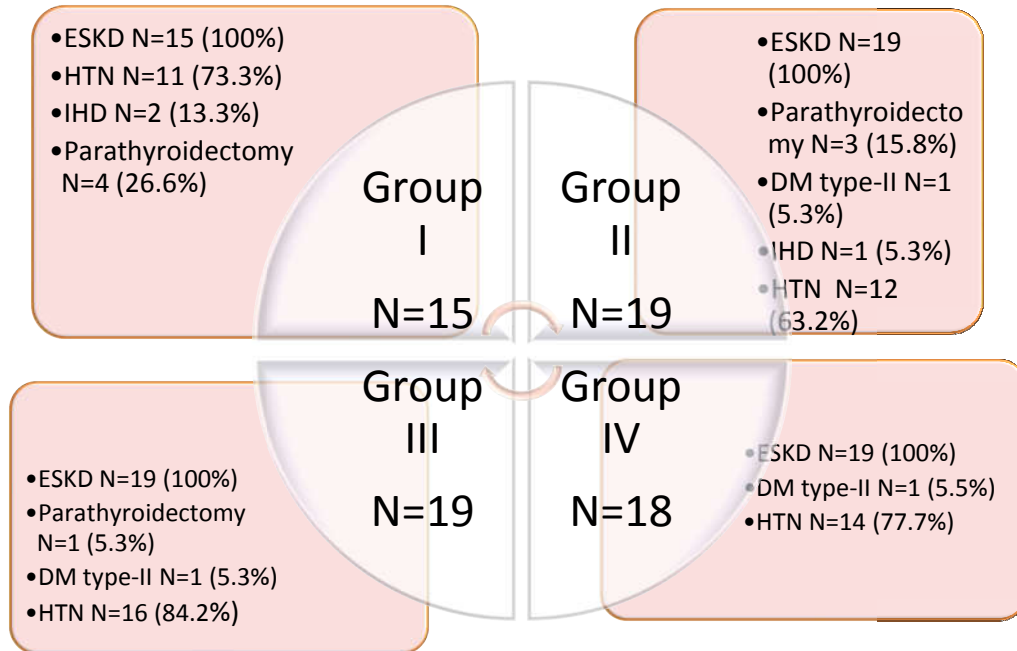


Figure 3: Patient's medical history of the HD participant patients presented as (percentage).

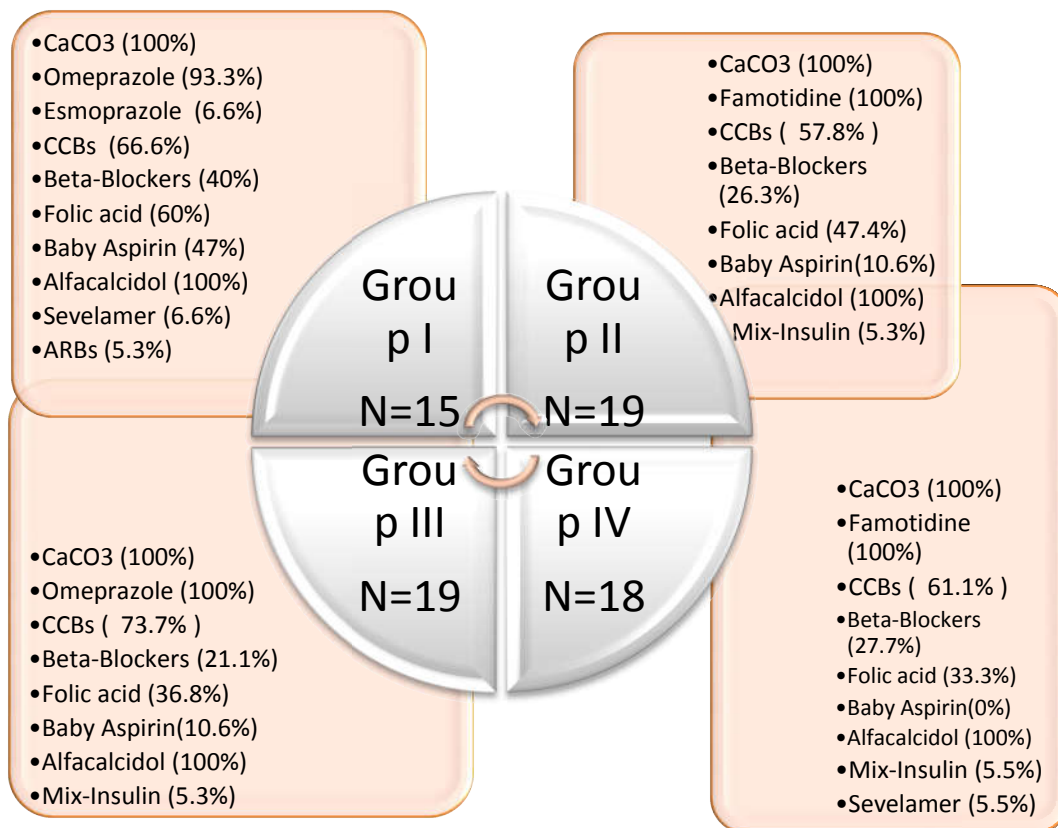


Figure 4: Current patient's medications history of the HD participant patients presented as(percentage).

Table 2: Demographic characteristics of the four studied group.

Characteristics		Group I N=15 Mean ±SEM	Group II N=19 Mean ±SEM	Group III N=19 Mean ±SEM	Group IV N=18 Mean ±SEM	Total N=71 Mean ±SEM	P- Value	Sig
Age (years)	KHMC	41.86±2.41	39.47±2.47	38.68±2.32	43.21±2.01	40.81±2.31	0.349	NS
Sex	Male (%)	8 males (53.33%)	7 males (36.84%)	12 males (63.16%)	10 males (55.55%)	37 males (52.11%)	0.438	NS
	Female (%)	7 females (46.66%)	12 females (63.16%)	7 females (36.84%)	8 females (44.44%)	34 females (47.89%)		
BMI (kg/m ²)	KHMC	25.2±0.057	22.21±0.043	25.26±0.040	26.51±0.039	24.79±0.043	0.897	NS
-Data are presented as Mean difference ±SEM or as percentage by using One-Way ANOVA test (at p-value< 0.05) S*: Significant -NS: Non significant-BMI: Body mass index -KHMC: King Hussein Medical								

Table 3: Other demographic characteristics of the four studied group.

Characteristics		Group I N=15 Mean± SEM	Group II N=19 Mean± SEM	Group III N=19 Mean± SEM	Group IV N=18 Mean± SEM	Total N=71 Mean± SEM	P-Value	Sig
Duration of dialysis (months)		127.33±22.787	97.68±15.338	64.63±6.642	93.44±11.628	94.03±7.496	0.036	S*
Duration of using CaCO ₃ tab as phosphate binder (months)		127.33±22.787	97.68±15.338	64.63±6.642	93.44±11.628	94.03±7.496	0.036	S*
Duration of using either PPIs or H2-Blockers (months)		99.33±24.484	75.47±11.136	64.63±6.642	90.33±11.998	81.38±6.945	0.315	NS
HD duration per session (hours)		4.27±0.137	4.18±0.109	3.97±0.060	4.08±0.061	4.12±0.047	0.158	NS
HD frequency per week (%)	1*per week	0 patient (0%)	1 patient (5.3%)	0 patient (0%)	0 patient (0%)	1 patient (1.4%)	0.313	NS
	2*per week	7 patients (46.7%)	5 patients (26.3%)	2 patients (10.5%)	5 patients (27.8%)	19 patients (26.8%)		
	3*per week	7 patients (46.7%)	13 patients (68.4%)	17 patients (89.5%)	13 patients (72.2%)	50 patients (70.4%)		
	4* per week	1 patient (6.7%)	0 patient (0%)	0 patient (0%)	0 patient (0%)	1 patient (1.4%)		
- Data are presented as Mean difference ±SEM or as percentage by using One-Way ANOVA test (at p-value< 0.05). - S*: Significant -NS: Non significant								

Table 4: Tested variables differences within the comparative groups.

Comparative Groups	Group I after Versus Group I before	Group II after Versus Group II before	Group III after Versus Group III before	Group IV after Versus Group IV before
Affective Variables				
SNAQ score (4-20)	+3 (4) (S*)	+4 (5) (S*)	+1 (6) (NS)	0 (3) (NS)
ALB (g/dl)	+0.43 ± 0.12 (S*)	+0.56 ± 0.11 (S*)	+0.21 ± 0.16 (NS)	+0.18 ± 0.23 (NS)
BUN (mg/dl)	+12.03 ± 5.75 (S*)	+14.34 ± 6.21 (S*)	+4.39 ± 9.17 (NS)	+4.21 ± 5.94 (S*)

-Data are presented as Mean difference ±SD or as median difference (Range) and are analyzed by using Paired T-Test or Wilcoxon Signed Ranks Test (at p-value<0.05).
 - S*: Significant -NS: Non significant
 -ALB: Albumin level.
 -BUN: Blood urea nitrogen.
 -SNAQ score (4-20): Simplified Nutritional Appetite Questionnaires score (4-20).

Table 5: Tested variables differences between the comparative groups.

Comparative Groups	Group I Versus Group II	Group I Versus Group III	Group I Versus Group IV	Group II Versus Group III	Group II Versus Group IV	Group III Versus Group IV
Affective Variables						
SNAQ score (4-20)	-1 (6) (NS)	+3 (8) (S*)	+3 (6) (S*)	+4 (10) (S*)	+4 (5) (S*)	0 (7) (NS)
ALB (g/dl)	-0.20 ± 0.13 (NS)	+0.44 ± 0.19 (S*)	+0.41 ± 0.15 (S*)	+0.62 ± 0.22 (S*)	+0.55 ± 0.18 (S*)	+0.10 ± 0.19 (NS)
BUN (mg/dl)	-2.317 ± 2.413 (NS)	+7.632 ± 2.413 (S*)	+7.818 ± 2.442 (S*)	+9.949 ± 2.266 (S*)	+10.135 ± 2.298 (S*)	+0.186 ± 2.298 (NS)

-Data are presented as Mean difference ±SEM or as median difference (Range) and are analyzed by using Tukey Kramer post-hoc multiple comparison analysis (at p-value< 0.05) and post-hoc multiple comparison analysis using Mann-Whitney U-test and bonferroni correction (at p<0.05)-Significant -NS: Non significant -ALB: Albumin level. -BUN: Blood urea nitrogen. SNAQ score (4-20): Simplified Nutritional Appetite Questionnaires score (4-20).

DISCUSSION:

Protein energy wasting (PEW) is a condition in which visceral protein and fat stores decrease as a result of many chronic co-morbid conditions, including chronic kidney disease¹¹⁻¹². Since PEW has been shown to be associated with a poor outcome in many clinical investigations, strategies to combat PEW have been anticipated and discussed¹³. Many factors are responsible for inadequate nutrient intakes in dialysis patients, among which anorexia and acid gastrointestinal disorders are more prevalent in dialysis patients. The significant increase of SNAQ score (4-20), ALB, and BUN in this study may be explained by the effects of Mg⁺² (from CaCO₃/MgCO₃ combination chewable tablets) on the gastrointestinal tract (GIT). Mg⁺² has a laxative effect in contrast to Ca⁺² that has a constipating effect which subsequently increases the intestinal peristalsis and gastric emptying.

Also, the CaCO₃/MgCO₃ combination chewable tablets (Rennie[®]) is approved by Food and Drug Administration (FDA) for indications of heartburn,

upset stomach, gastric pain, feeling of epigastric heaviness or fullness and nausea which may improve appetite in HD patients and subsequently minimize the progression of PEW. The significant parallel increasing of ALB and BUN levels with SNAQ score (4-20) indicates an appetizing effect of CaCO₃/MgCO₃ combination chewable tablets when compared with CaCO₃ tablets that is more significant when the CaCO₃/MgCO₃ combination chewable tablets were co-administered with H₂-Blockers than PPIs (+4 (5) vs +3 (8)). In this study, we revealed that CaCO₃/MgCO₃ combination chewable tablet had a significant appetizing effect in HD patients when it replace CaCO₃ tablet as phosphate binder especially when the acid suppressing agent is H₂-Blockers. The appetizing effect of our interventional phosphate binder may improve the nutritional status of HD patients as observed in this study by significant increase in ALB which may have a positive impact on both quality of life and mortality of HD patients. The shortcoming of our study is that there was no washout period in this study and the sample size was small and should be increased.

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