

## ORIGINAL RESEARCH

**THE EFFECTS OF CALCIUM CARBONATE/MAGNESIUM CARBONATE COMBINATION CHEWABLE TABLETS IN COMPARISON TO CALCIUM CARBONATE TABLETS ON PHOSPHATE BINDING IN HEMODIALYSIS PATIENTS WHO ARE TAKING PROTON PUMP INHIBITORS**

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**ABSTRACT:**

Calcium carbonate/magnesium carbonate combination chewable tablets may be an alternative phosphate binder to calcium carbonate tablets with suspected potential advantages of synergistic phosphate binding. The major limitation of calcium carbonate phosphate binding capacity in hemodialysis patients (HD) is the co-administration of acid-suppressing drugs like proton pump inhibitors which slow the dissolution rate of calcium carbonate tablet and decrease its phosphate binding capacity.

**Methods:** Randomized, controlled, open label study was conducted at renal /hemodialysis unit of King Hussein Medical Center and Jordan University Hospital for six weeks aimed to evaluate the differences between CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets and CaCO<sub>3</sub> tablets on 36 HD patients who are taking PPIs in terms of serum PO<sub>4</sub><sup>3-</sup> level and serum Mg<sup>+2</sup>.

In this study, we revealed that CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets had a significantly more effectiveness in reducing the serum PO<sub>4</sub><sup>3-</sup> level at the cost of significantly more increase in serum Mg<sup>+2</sup> level than CaCO<sub>3</sub> tablets when both CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets and CaCO<sub>3</sub> tablets were combined with PPIs.

**KEYWORDS:** calcium carbonate, magnesium carbonate, phosphate, tablet

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**INTRODUCTION:**

Healthy kidneys are very necessary for cells functioning by maintaining the extracellular environment. This is achieved by specifically adjusting the urinary excretion of water and electrolytes to match net intake and excretion of wasteproducts of metabolism, such as creatinine, urea, and uric acid<sup>1</sup>.

When the amount of functioning kidney tissue is greatly diminished, chronic kidney disease (CKD) will develop. End-stage renal disease (ESRD) is reached when the renal function drops below 10 to 15 percent of the normal function<sup>2</sup>.

Unless renal replacement therapy is started when ESRD occurs, it rapidly leads to death<sup>3</sup>. The most common type is hemodialysis (HD), in which waste products are removed from the body by diffusion mechanism across a non-biological semipermeable membrane in an artificial kidney. HD is usually performed at a dialysis center from two to three times per week for three to four hours<sup>4</sup>.

Phosphorus serum levels are usually within normal range until the GFR falls below approximately 30 ml/min according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF:K/DOQI) classification<sup>5</sup> and with continuing phosphate ingestion, reducing bone uptake of phosphate or increasing release of phosphate from high turnover bone hyperphosphataemia will occur.

Administration of dietary phosphorus binders in attempt to block intestinal. In addition, stage 5 chronic kidney disease patients were recommended to undergo hemodialysis to facilitate phosphates removal from blood that was already absorbed. However, four decades after the introduction of chronic hemodialysis in early 1960s, we have not yet found the ideal phosphate binder(s) in terms of combined efficacy, safety, availability, disintegration time, low pill burden, activity over a wide pH range, and low cost. There are multiple pharmacological options available for use as phosphate binders. Many studies assessing the efficacy and safety of these agents are available<sup>6</sup>.

Magnesium carbonate ( $MgCO_3$ ) and magnesium hydroxide [ $Mg(OH)_2$ ] have been administered either alone or in combination with calcium salts with good results<sup>7</sup>. As renal function further deteriorates to CKD Stages 4 and 5, the quantitative excretion of magnesium tends to decrease and cannot be compensated any longer by an increased fractional excretion of magnesium<sup>8</sup>. This first becomes apparent as

creatinine clearance falls <30 mL/min and particularly <10–15 mL/min. Thus, overt hypermagnesaemia develops frequently in patients with creatinine clearances <10 mL/min. As such, renal failure patients might be more vulnerable to changes in magnesium intake via the diet or via medication (e.g. antacids or phosphate binders)<sup>9</sup>, so that these compounds are not widely used in ESRD patients because nephrologists have an inordinate fear of hypermagnesemia and the belief that Mg administration frequently is accompanied by

pH affects both the rate of dissolution of the salt and the subsequent binding reaction between the metal ion and phosphate. Generally, a very acidic pH is best to dissolve and ionize the salt<sup>10</sup>. Then, the metal ion must combine with inorganic phosphorus and this reaction may also be pH dependent. The optimal pH for these two reaction steps may be very different. For example,  $CaCO_3$  is most soluble at pH 1 to 3, but calcium to phosphate binding is optimal above pH 5<sup>11</sup>. Ionized calcium binding to phosphorus is very pH dependent and decreases sharply below pH 5, so that  $CaCO_3$ , the most widely used calcium salt, dissolves best in a very acid milieu and thus hypo or achlorhydria caused by using either  $H_2$ -Blockers<sup>12</sup> or proton pump inhibitors (PPIs)<sup>13</sup> would compromise  $CaCO_3$  tablet dissolution and reduce its efficacy as a phosphorus binder.

Chronic renal failure and particularly end stage renal failure are frequently accompanied by gastro-duodenal ulcers and erosive gastritis secondary to gastro-esophageal reflux. The use of gastric acid secretion inhibitors is the base for the treatment of these complications. Therefore, the use of  $H_2$ -Blockers or PPIs would compromise  $CaCO_3$  tablet dissolution and reduce its efficacy as a phosphorus binder<sup>14</sup>.

Binaphos CM<sup>®</sup>, a Calcium carbonate/Magnesium carbonate ( $CaCO_3/MgCO_3$ ) combination phosphate binder that contains two phosphate-binding elements 291 mg of magnesium carbonate ( $MgCO_3$ ) and 340 mg of  $CaCO_3$  is marketed for treating elevated phosphate levels in dialysis patients but it has the disadvantage of high cost and unavailability in many countries. Although studies using  $CaCO_3/MgCO_3$  combination as a phosphate binder are short term with small numbers of patients, this phosphate binder has shown some promising results and may provide clinicians with an alternative for phosphate binding<sup>15</sup>.

Another  $CaCO_3/MgCO_3$  combination which is available in most countries with a low cost under the trade name of Rennie<sup>®</sup> is only

approved for indications of heartburn, upset stomach, gastric pain, feeling of epigastric heaviness or fullness, and nausea. CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet (Rennie<sup>®</sup>) is a chewable tablet with peppermint flavor, which contains 80 mg of MgCO<sub>3</sub> and 680 mg of CaCO<sub>3</sub> per tablet. In comparison to CaCO<sub>3</sub>/MgCO<sub>3</sub> combination tablet (Binaphos CM<sup>®</sup>), CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet (Rennie<sup>®</sup>) has a lower content of magnesium with a greater content of calcium, which may be a useful alternative to CaCO<sub>3</sub>/MgCO<sub>3</sub> combination tablet (Binaphos CM<sup>®</sup>) as a phosphate binder. In comparison to CaCO<sub>3</sub> tablet, CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet (Rennie<sup>®</sup>) has a greater dissolution rate after chewing or sucking the tablet and it may be less affected by alteration in stomach pH when co-administered with H<sub>2</sub>-Blockers or PPIs, since the use of H<sub>2</sub>-Blockers or PPIs would compromise CaCO<sub>3</sub> tablet dissolution and reduce its efficacy as a phosphorus binder<sup>16</sup>.

A phosphate binder combining a reduced calcium exposure and the possible beneficial effect of controlled magnesium administration, potentially offering the double advantage of favorable gastrointestinal tolerance and positive cardiovascular effects, seemed worthwhile to investigate for its phosphorus-lowering capacity<sup>17</sup>.

#### AIMS OF STUDY:

The aim of this study is to evaluate the differences between HD participants who are taking PPIs+CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets (Rennie<sup>®</sup>) (Group I) and HD participants who are taking PPIs + only CaCO<sub>3</sub> tablets (Group II) in terms of serum phosphate (PO<sub>4</sub><sup>-3</sup>) level and serum magnesium (Mg<sup>+2</sup>) level in the renal /hemodialysis unit of King Hussein Medical Center (KHMC) and Jordan University Hospital (JUH).

#### The Impact of Study:

Since, the patients with ESKD are frequently associated with gastro-duodenal ulcers and erosive gastritis, and the use of either H<sub>2</sub>-Blockers or PPIs are the base for the treatment of these complications, and since the using of these acid secretion inhibitors will compromise CaCO<sub>3</sub> tablet dissolution and reduce its efficacy as a phosphorus binder, it is important to minimize this interaction by increasing the dissolution rate of phosphate binder by increasing the surface area of contact between gastric content and phosphate binder

particles. This can be done by chewing or sucking a palatable tablet.

The CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet (Rennie<sup>®</sup>) is a chewable tablet with peppermint flavor, which contains 80 mg MgCO<sub>3</sub> and 680 mg CaCO<sub>3</sub>, so that chewing or sucking two tablets of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet after a meal will be almost equal in mg basis of calcium content to swallowing one tablet of CaCO<sub>3</sub> 1250 mg with a meal. In addition, the 80 mg of MgCO<sub>3</sub> in CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet may add an additional phosphate binding activity to the 680 mg of CaCO<sub>3</sub> due to magnesium phosphate binding effect.

This study is important to identify if CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets (Rennie<sup>®</sup>) have a superior efficacy and/or safety as phosphate binder without increased risk of hypermagnesemia in comparison to CaCO<sub>3</sub> tablets in HD patients who are taking PPIs.

#### METHODS

##### Study design:

Randomized, controlled, open label study was conducted at renal /hemodialysis unit of KHMC and JUH, Amman, Jordan. HD patients were randomly allocated into interventional groups (Group I) or control groups (Group II) after they accepted to participate in this study.

All possible retrospective data for Group I and Group II were collected before the study period was started. The retrospective data that we collected (data of three months ago for HD participants in renal /hemodialysis of JUH and KHMC), included the last three values of serum PO<sub>4</sub><sup>-3</sup> levels, serum Mg<sup>+2</sup> levels, and the number of CaCO<sub>3</sub> tablets per day (N<sub>1</sub>) in addition to the baseline values of these parameters

After retrospective data were completed, the two studied groups were followed for 6 weeks in which the following outcomes were measured or assessed in the following basis:

- Serum PO<sub>4</sub><sup>-3</sup> level was measured on weekly basis for the first 2 weeks and then every other week.
- N<sub>1</sub> and the number of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets (Rennie<sup>®</sup>) per day (N<sub>2</sub>) were measured on daily basis.

The CaCO<sub>3</sub> tablets in Group I were replaced by CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets (Rennie®) without a washout period (maximum 6 tablets per day), in which each 1 tablet of CaCO<sub>3</sub> 1250 mg was replaced by 2 tablets of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination 680 mg/80 mg (Rennie®), while keeping all other medications without any change (Including PPIs). If serum Mg<sup>+2</sup> level was ≥3.5 mg/dl and persisted for 1 week or serum Mg<sup>+2</sup> level was ≥4.5 mg/dl, we dropped-out the HD participant from our study. The CaCO<sub>3</sub> tablets in Group II was kept without any change in the prospective follow-up phase.

#### **Ethical approval:**

The study was approved by the Scientific Committee of the Faculty of Pharmacy/The University of Jordan and the Faculty/Postgraduate Studies at the University of Jordan, In addition to ethical approval from the IRB committees at the Jordanian Royal Medical Services and JUH.

#### **Study setting:**

The patients in the renal /hemodialysis unit of KHMC and JUH who did not meet the inclusion and didn't meet the exclusion criteria were enrolled in this study and after they signed an informed consent form, all were randomly allocated into either interventional group (Group I) or control group (Group II) (www.randomization.com). Then, the data collection took place after the patients accepted to participate into the study.

#### **Sample size:**

The sample size of this study was a convenient sample. The total sample size was 36 HD participants, 13 HD participants were from renal /hemodialysis unit of JUH and 23 HD participants were from renal /hemodialysis unit of KHMC.

#### **Study subjects:**

The study subjects included all HD participants in the renal /hemodialysis unit of KHMC and JUH who did not meet the inclusion criteria and didn't meet the exclusion criteria and who accepted to participate in this study after consent form signing and random allocation into the four different study groups.

#### **Inclusion Criteria:**

The inclusion criteria for HD participants in this study included: Age greater than 18 years, age lower than 60 years, on chronic hemodialysis for at least three months, the HD participants used CaCO<sub>3</sub> tablets as a phosphate binder and used PPIs as an acid-suppressive agents for at least 3 months before participating in this study.

#### **Exclusion Criteria:**

The exclusion criteria for HD patients in this study included: Serum cCa<sup>+2</sup> level above 10.2 mg/dl, cCa<sup>+2</sup>×PO<sub>4</sub><sup>-3</sup> above 55 mg<sup>2</sup>/dl<sup>2</sup>, serum Mg<sup>+2</sup> baseline level above 3.5 mg/dl, there was a positive history of psychiatric or other disorders leading to compliance issues, and there was a positive history of dysphagia or swallowing disorders or bowel obstruction.

#### **Procedures:**

Blood samples were drawn from the HD participants before HD session and heparin infusion were started. The tests of serum PO<sub>4</sub><sup>-3</sup> and serum Mg<sup>+2</sup> were performed within 1-2 hours after the unheparinized blood was immediately separated by centrifugation in the KHMC and JUH chemistry laboratories. The N<sub>1</sub> and N<sub>2</sub> were obtained directly from HD participants.

#### **Data analysis**

After follow-up part of this open label randomized controlled trial was finished at the end of 6 weeks. The collected data of each outcome in the different two studied groups were analyzed using SPSS software release 20.0.

Un-Paired t test analysis was used to present the demographic characteristics of age (years), body surface area (BSA) (m<sup>2</sup>), body mass index (BMI) (kg/ m), duration of dialysis (months), duration of using CaCO<sub>3</sub> tablets as phosphate binder (months), duration of using PPIs (months) and HD duration per session (hours) by comparing the mean±SD among groups. In case of gender (male or female) and HD frequency per week (%) data were presented as percentage of frequency.

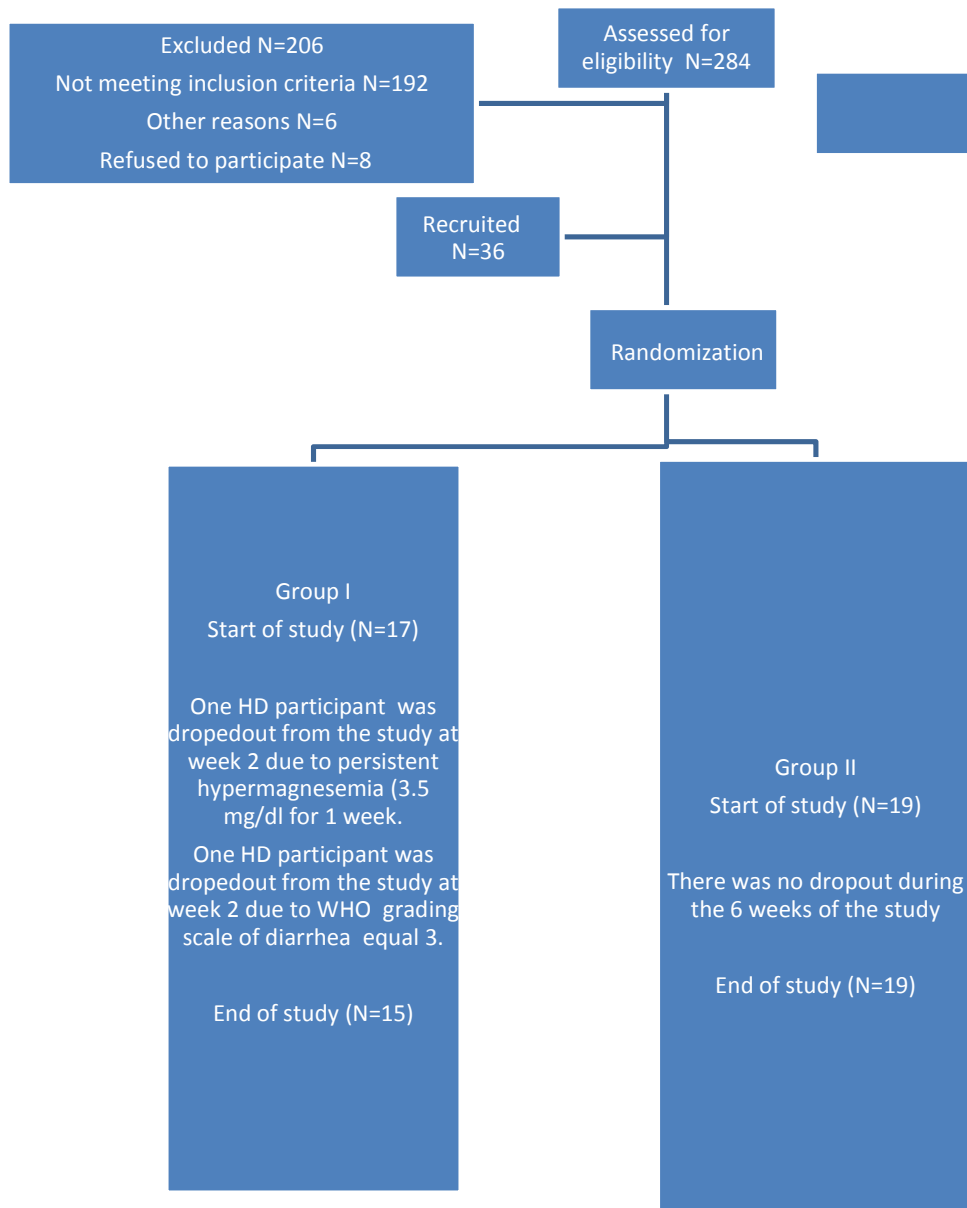
Unpaired t test was also used to analyze the serum PO<sub>4</sub><sup>-3</sup> level and serum Mg<sup>+2</sup> level by comparing the mean difference ±SD among two groups.

#### **RESULTS:**

Sample characteristics:

Recruitment process:

The recruitment, randomization, and dropout processes are summarized in Figure (1).



**Figure 1:** Recruitment, randomization, and dropout processes scheme.

## Demographics:

All demographic characteristics of 34 HD participants in the four studied groups are summarized in Tables (1-2).

**Table 1:** Demographic characteristics of the four studied groups.

Characteristics		Group I N=15 Mean±SD	Group II N=19 Mean±SD	Total N=34 Mean±SD	P- Value	significance	
Age (years)	KHMC	41.86±2.41	38.68±2.32	40.81±2.31	0.349	NS	
	JUH	39.86±2.86	30.68±2.97	34.84±2.55			
sex	Male (%)	KHMC	5 males (62.5%)	8 males (66.6%)	0.438	NS	
		JUH	3 males (37.5%)	4 males (33.3%)			16 males (43.2%)
	Female (%)	KHMC	4 females (57.1 %)	5 females (71.4 %)			26 females (76.5 %)
		JUH	3 females (42.8 %)	2 females (28.6 %)			8 females (23.5 %)
BMI (kg/m <sup>2</sup> )	KHMC	25.2±0.057	25.26±0.040	24.79±0.043	0.897	NS	
	JUH	23.2±0.097	21.20±0.041	22.27±0.053			

Data are presented as Mean difference ±SD or as percentage by using Unpaired t-test (at  $p$ -value < 0.05)  
S\*: Significant -NS: Non significant-BMI: Body mass index -KHMC: King Hussein Medical Center -JUH: Jordan University Hospital

**Table 2: Other demographic characteristics of the four studied groups.**

Characteristics		Group I N=15 Mean± SD	Group II N=19 Mean± SD	Total N=34 Mean± SD	P-Value	Significance
Duration of dialysis (months)		127.33± 22.787	64.63± 6.642	94.03± 7.496	0.036	S*
Duration of using CaCO <sub>3</sub> tab as phosphate binder (months)		127.33± 22.787	64.63± 6.642	94.03± 7.496	0.036	S*
Duration of using either PPIs or H2-Blockers (months)		99.33± 24.484	64.63± 6.642	81.38± 6.945	0.315	NS
HD duration per session (hours)		4.27± 0.137	3.97± 0.060	4.12± 0.047	0.158	NS
HD frequency per week (%)	1*per week	0 patient (0)	0patient (0%)	1 patient (1.4%)	0.313	NS
	2*per week	7patients (46.7%)	2patients (10.5%)	19 patients (26.8%)		
	3*per week	7patients (46.7%)	17patients (89.5%)	50 patients (70.4%)		
	4* per week	1 patient (6.7%)	0 patient (0%)	1 patient (1.4%)		

Data are presented as Mean difference ±SD or as percentage by using Unpaired t- test (at  $p$ -value < 0.05)

- S\*: Significant    -NS: Non significant

Patients medical history:

The HD patient's medical history in each group of the four studied groups are summarized in Figure (2).

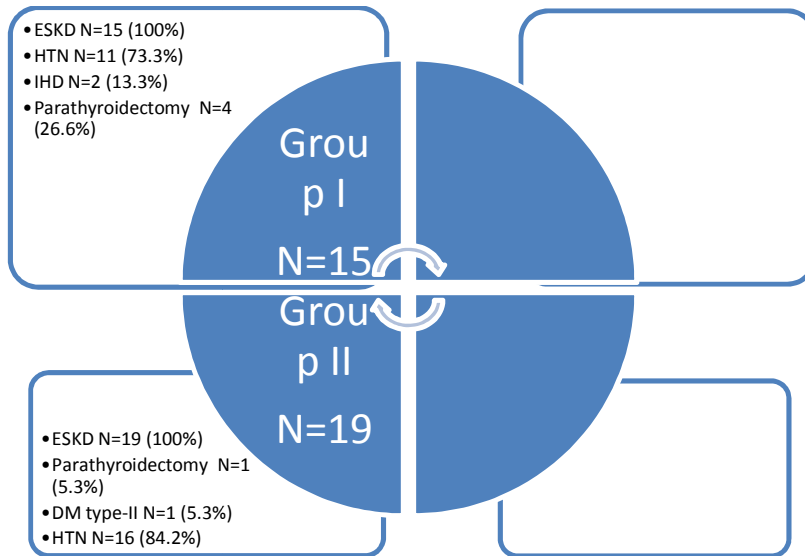


Figure 2: Patient's medical history of the HD participant patients presented as (percentage).

Patient's medications before starting the study:

The HD patient's medications in each group of the four studied groups are summarized in Figure (3).

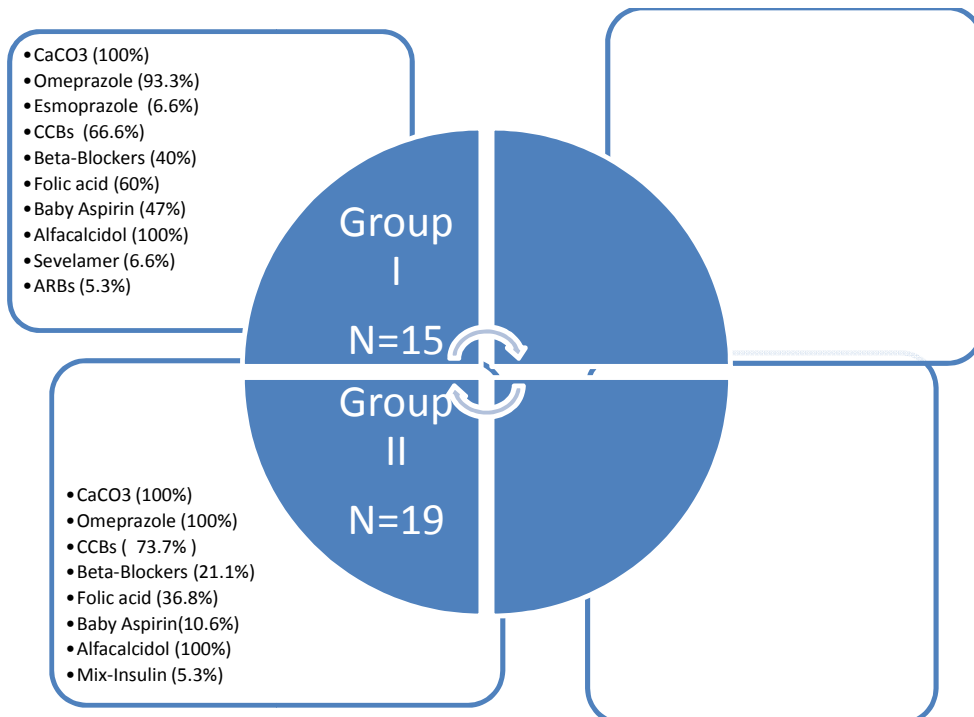


Figure 3: Current patient's medications history of the HD participant patients presented as (percentage).



Between and within groups comparisons of serum  $\text{PO}_4^{3-}$  levels. Results of serum  $\text{PO}_4^{3-}$  levels analysis between the two studied groups are summarized in Tables (3).

**Table 3:** Between and within groups comparisons results of serum  $\text{PO}_4^{3-}$  levels.

Interval	Group I N=15 Mean±SD	Group II N=19 Mean±SD
Before	4.79±1.21	4.79±0.83
After	3.79±1.16	4.73±0.81
Differences	-0.99±0.57	-0.06±0.46
<i>p</i> -value (Significance)	0.000* S*	0.593 NS
Between groups comparisons	-0.936±0.224	
<i>p</i> -value (significance)	0.001(S*)	

Data are presented as Mean±SD and are analyzed by using Paired T-Test. Also, the between groups data are analyzed by using Unpaired T- Test.

- S\*: Significant    -N: Number of HD participants    -NS: Non significant    - $\text{PO}_4^{3-}$ : phosphate

Between and within groups comparisons of  $\text{Mg}^{+2}$  levels. Results of serum  $\text{Mg}^{+2}$  levels analysis between and within two studied groups are summarized in Tables (4-5).

**Table 4:** Between and within groups comparisons results of serum  $\text{Mg}^{+2}$  level.

Interval	Group I N=15 Mean±SD	Group II N=19 Mean±SD
Before	2.15±0.29	2.12±0.33
After	2.45±0.32	2.16±0.24
Differences	+0.30±0.34	+0.05±0.17
<i>p</i> -value (Significance)	0.004 S*	0.218 NS
Between groups comparisons	+0.254±0.094	
<i>p</i> -value (significance)	0.042 S*	

Data are presented as Mean±SD and are analyzed by using Paired T-Test. Also, the between groups data are analyzed by using Unpaired T-Test.

- S\*: Significant    -N: Number of HD participants    - $\text{Mg}^{+2}$ : Magnesium    -NS: Non significant

**Table5:** Serum PO<sub>4</sub><sup>3-</sup> levels and the related variables values differences within the comparative groups.

Comparative Groups Affective Variables	Group I after Versus Group I before	Group II after Versus Group II before	Group I Versus Group II
Serum PO <sub>4</sub> <sup>3-</sup> level (mg/dl) Mean difference ±SD (Sig)	-0.99 ±0.57 (S*)	-0.06 ±0.46 (NS)	-0.936 ± 0.224 (S*)
Serum Mg <sup>2+</sup> level Mean difference ±SD(Sig)	+0.30±0.34 (S*)	+0.05±0.17 (NS)	+0.254±0.094 (S*)
n <sub>1</sub> (tablet/day) Mean difference ±SD(Sig)	-2.335 ±0.515 (S*)	+0.026 ±0.115 (NS)	-2.36 ± 0.16 (S*)
n <sub>2</sub> (tablet/day) Mean difference ±SD(Sig)	+4.431 ±1.119 (S*)	0	+4.43 ± 0.26 (S*)
CaCO <sub>3</sub> (mg/day) Mean difference ±SD (Sig)	+93.686 ±630.21 (NS)	+32.894 ±143.385 (NS)	(NS)
MgCO <sub>3</sub> (mg/day) Mean difference ±SD(Sig)	+354.45 ±89.55 (S*)	0	+354.45 ± 20.49 (S*)

Data are presented as Mean difference ±SD or as median difference (Range) and are analyzed by using Paired T-Test, Unpaired T-Test (at p-value<0.05).

- S\*: Significant -NS: Non significant

- n<sub>1</sub> (tablet/day): Number of CaCO<sub>3</sub> tablets per day that were used as phosphate binder.

-n<sub>2</sub> (tablet/day): Number of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets per day.

-CaCO<sub>3</sub> (mg/day): Amount of CaCO<sub>3</sub> in mg per day from either CaCO<sub>3</sub> tablets that were used as phosphate binder or from CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets or from both.

MgCO<sub>3</sub> (mg/day): Amount of MgCO<sub>3</sub> in mg per day from CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets.

#### DISCUSSION:

The effects of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets versus CaCO<sub>3</sub> tablets on study parameters:

This study revealed that when CaCO<sub>3</sub> tablets were replaced by CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablets. The serum PO<sub>4</sub><sup>3-</sup> level was decreased significantly while the serum Mg<sup>2+</sup> level was increased significantly.

These results were explained depending on the pH effects on dissolution and binding kinetic of CaCO<sub>3</sub> tablet which can be summarized by "

The acidity is best for solubility, but binding to phosphorus is best at higher pH because at a low pH the higher H<sup>+</sup> concentration effectively competes with ionized calcium for binding to phosphorus<sup>11</sup>. So, when the CaCO<sub>3</sub> tablets are taken with PPIs, the pH of stomach will be elevated and the acidity that is necessary to dissolve the CaCO<sub>3</sub> tablet will be decreased and then the phosphate binding capacity of CaCO<sub>3</sub> tablet will be decreased in contrast of CaCO<sub>3</sub>/MgCO<sub>3</sub> combination chewable tablet, there is no problem in dissolution after either chewing or sucking and so that, there is no drug interaction with PPIs on the dissolution step (rate-limiting step), in addition to that, the

higher pH in stomach that is created by PPIs will potentiate the second step of phosphate binding scenario (binding of  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$  to the  $\text{PO}_4^{-3}$  in the GIT). Furthermore, intestinal absorption of magnesium can also be influenced by calcium and vice versa<sup>16</sup>. High intestinal calcium concentrations have been reported to reduce the absorption of magnesium and subsequently reduce the risk of hypermagnesemia<sup>17</sup>.

#### CONCLUSIONS:

-Calcium Carbonate/Magnesium Carbonate ( $\text{CaCO}_3/\text{MgCO}_3$ ) combination chewable

tablets had a significantly more effectiveness than  $\text{CaCO}_3$  tablets in reducing the serum  $\text{PO}_4^{-3}$  level when  $\text{CaCO}_3/\text{MgCO}_3$  combination chewable tablets replace  $\text{CaCO}_3$  tablets were combined with PPIs.

-Calcium Carbonate/Magnesium Carbonate ( $\text{CaCO}_3/\text{MgCO}_3$ ) combination chewable tablets had a significantly more increase in serum  $\text{Mg}^{+2}$  level than  $\text{CaCO}_3$  tablets when both  $\text{CaCO}_3/\text{MgCO}_3$  combination chewable tablets and  $\text{CaCO}_3$  tablets were combined with PPIs.

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