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Original article

# Effect of Control of Secondary Hyperparathyroidism and Hyperphosphatemia on Slowing Chronic Kidney Disease Progression

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## Abstract:

**Background:** Chronic Kidney Disease (CKD) is a progressive disease which takes from months to years depending on many factors. Treatment of CKD aims at slowing progression as long as possible with better quality of life. Hyperphosphatemia and secondary hyperparathyroidism (SHPT) are major complications of CKD. They have been associated with higher morbidity and mortality, which led to the assumption that their correction could reduce complications and CKD progression. **Aim:** to study the possible role of controlling of secondary hyperparathyroidism and hyperphosphatemia on slowing progression of chronic kidney disease in patients with chronic kidney disease stage 3 and stage 4.**Materials & Methods:** This prospective cohort multicenter study included 200 patients with stage 3–4 CKD; recruited from nephrology departments and outpatient clinics in Benha university hospitals and Benha health insurance hospital. Participants underwent baseline measurement of CKD-MBD biomarkers and updated at each study visit, scheduled at a monthly interval over a 6-month follow-up. Ethical guidelines of our institutions were considered and consent was obtained from participants .**Results:** In this study on 200 CKD patients of stage 3-4, it was found that the lower phosphate and PTH levels at the initial measurement and after 6 months were significantly associated with slower CKD progression. In addition, the use of cinacalcet, phosphate binders and alphacalcidol were significantly associated with slower CKD progression. **Conclusion:** The control of secondary hyperparathyroidism (SHPT) and hypophosphatemia are independently associated with slowing chronic kidney disease progression in CKD patients' stage 3-4, which encourages their early control to delay loss of renal function in this population.

**Keywords:** CKD progression; Hyperphosphatemia; Secondary hyperparathyroidism.

## Introduction

Chronic kidney disease is defined as abnormalities in kidney structure and function present for at least three months. [1]

CKD is a progressive disease in which progression takes from months to years depending on many factors e.g.: etiology, exposure, interventions. [2] Periodic follow up of CKD patients' progression is necessary. Early diagnosis of CKD in asymptomatic individuals can help to start treatment early aiming to slow progression of CKD or its complications as cardiovascular diseases and thus improving morbidity and mortality. [3]

Risk factors of chronic kidney disease progression include many comorbid conditions such as cardiovascular diseases (CVD), Hypertension [4], Proteinuria [5], Anemia [6], Mineral and bone disorders [7], Dyslipidemia [8]. Measures to slow CKD progression involves the dietary and lifestyle modifications as plant dominant low protein diet, physical activity, weight reduction, smoking cessation and salt restriction. [9]

In addition to lifestyle modification some drugs are used to slow progression of CKD such as blood pressure lowering agents including renin-angiotensin-aldosterone-system (RAAS) blockers, mineralocorticoid receptor antagonists. [10] Also sodium glucose transporter 2 inhibitors (SGLT2i) were found to be associated with less proteinuria and improved renal outcome, [11] and lipid lowering drugs as well. Hyperphosphatemia and secondary hyperparathyroidism are major complications of CKD. They have been associated with vascular calcification, cardiovascular events, and higher all-cause mortality rates. Multiple studies have documented the link between hyperphosphatemia and increased all-cause mortality and CVD in both healthy individuals and patients with CKD. [12]

Elevated PTH levels are associated with the risk of cardiovascular events irrespective of CKD stage, and in patients with non-dialysis CKD, PTH is a predictor of risk of fractures, vascular events, progression to dialysis and death. [13]

In patients with CKD stages 3–4, eGFR progressively decreases and there's an increasing lack of ability to efficiently excrete phosphate and prevent its retention. PTH acts on renal proximal tubular cells and down regulates phosphate transporters, thereby it leads to phosphaturia. Phosphate concentrations start to increase in spite of elevations in PTH, indicating that compensatory mechanisms are no longer enough to preserve phosphate balance and avoid hyperphosphatemia. [14]

Hypocalcaemia develops, and PTH responds through increasing bone turnover, leading to calcium and phosphate launch from bones, which in addition increases serum phosphate concentrations that continue to stimulate more hypocalcaemia and more release of PTH in an endless vicious cycle. [15]

Abnormal phosphate, calcium, FGF23, and PTH concentrations are independent risk factors for mortality, they're related to each other in a progressively worsening cycle. [16]

Early detection and treatment of secondary hyperparathyroidism (SHPT) is important. The treatment strategy is a combination of serum calcium correction, restriction of phosphorus in diet, phosphate binders, vitamin D and calcimimetics. [17] In case of secondary hyperparathyroidism (SHPT) refractory to medical treatment parathyroidectomy can be considered. [18]

Early hyperphosphatemia and SHPT identification and management has a vital role in the long term improvement of CKD, slowing progression, and prevention of complications as long as possible. [19]

**Aim of work**

The aim of this work was to study the possible role of controlling of secondary hyperparathyroidism and hyperphosphatemia on slowing progression of chronic kidney disease in

patients with chronic kidney disease stage 3 and stage 4.

## Patients and methods

The study protocol was in conformity with the ethical guidelines of our institutions, with approval number of the local ethical committee: MS36-11-2022, and consent was obtained from each participant.

**Patients**

Patients we included in this prospective cohort multicenter study are 200 patients with stage 3–4 CKD, recruited from nephrology departments and outpatient clinics in Benha university hospitals and Benha health insurance hospital. Patients were divided at enrollment into three groups:

Group 1: patients with secondary hyperparathyroidism (SHPT)

Group 2: patients with hyperphosphatemia

Group 3: patients with secondary hyperparathyroidism (SHPT) and hyperphosphatemia

The patients were further divided into 6 subgroups according to the group and the CKD stage.

Group 1A: patients with secondary hyperparathyroidism (SHPT) – CKD Stage 3

Group 2A: patients with hyperphosphatemia – CKD stage 3

Group 3A: patients with secondary hyperparathyroidism (SHPT) and hyperphosphatemia – CKD stage 3

Group 1B: patients with secondary hyperparathyroidism (SHPT) – CKD stage 4

Group 2B: patients with hyperphosphatemia – CKD stage 4

Group 3B: patients with secondary hyperparathyroidism (SHPT) and hyperphosphatemia – CKD stage 4

Patient enrolment was performed between April 2023 and April 2024. The study contemplated six visits over a 6-month follow-up. The inclusion criteria include age more than 18 years, the patient is classified within stages 3 and 4 as defined by KDIGO CKD 2012 classification according to eGFR (stage 3: 30-59, stage 4: 15-29) (20), stable clinical condition and no infections or acute inflammatory process. The exclusion criteria include Patients on hemodialysis, Pregnancy, Malignancy.

**Laboratory measurements**

At enrollment, patients underwent clinical assessment of Blood Pressure (BP), BMI and Laboratory investigations of HbA1c, Lipid profile, Serum creatinine , Albumin-to-creatinine ratio (ACR), Hemoglobin level, Serum Calcium, Serum phosphate, PTH, Alkaline phosphatase.

(eGFR) was calculated from serum creatinine level using (Chronic Kidney Disease Epidemiology Collaboration equation) (CKD-EPI), mL/min per 1.73m2. (21) Participants underwent baseline measurement of CKD-MBD biomarkers and updated at each study visit, scheduled at a monthly interval, which include: Calcium, Phosphorus, PTH and eGFR.

Patients were followed for 6 months or until kidney transplantation, death, refusal for further participation or loss to follow-up.

**Statistical analysis**

The collected data was revised, coded, and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Mean, standard deviation (± SD), median, and range were used for numerical data. Frequency and percentage were used for non-numerical data. A p value is considered significant if <0.05 at confidence interval 95%.

## Results

As shown in (Table 1), the demographic data of the studied cohort (N=200) reveals a nearly equal distribution of male (41.5%) and female (58.5%) participants. The mean age of the cohort is 56.87 years

(SD=10.97), with a median age of 57 years. The age range spans from 26 to 76 years.

Among the blood chemistry parameters in the cohort the mean levels of phosphorus, calcium, Alkaline phosphatase (ALP), Hb, and PTH are recorded, with varying ranges and interquartile ranges. Phosphorus levels range from 2.8 to 6.4 mg/dL, while calcium levels span from 6.2 to 10.3 mg/dL. ALP levels average at 82.83 IU/L with a range of 45-160 IU/L, PTH levels vary from 55 pg/ml to 1100 pg/ml, with a mean of 213.69 pg/ml.

The table outlines comorbidities within the studied cohort, with DM and dyslipidemia being prevalent among 40.0% and 60.0% of the cases, respectively. FBG levels range from 90 to 165 mg/dL. Regarding Lipid profile, dyslipidemia was found in 60% of patients with TC levels range from 110 to 260 mg/dL, LDL levels range from 59 to 158 mg/dL, HDL levels range from 32 to 60 mg/dL, TG levels range from 91 to 251 mg/dL.

Regarding initial renal function tests, eGFR levels average at 30.25, with a range of 15-54 and a median value of 30. The cohort is evenly split between CKD Stage grades 3 and 4, each accounting for 50% of cases. In terms of treatment received, a majority (84.0%) have been prescribed Alpha calciol, while 64.0% have been given phosphate binders. Cinacalcet has been administered to 5.0% of participants.

The demographic characteristics were relatively balanced between the groups. Regarding eGFR there was trend to increase across time points, with significant differences in eGFR across the six months in the three groups. No significant differences were found between the slow and rapid progression regarding age and gender.

Phosphorus levels range from 2.8 to 6.4 mg/dL. The lower phosphate level at the initial measurement and after 6 months were significantly associated with slower eGFR decline ($P<0.05$) (Table 2) (fig. 1). PTH levels vary from 55 to 1100, with a mean of 213.69. The lower PTH levels initially and after 6 months were significantly associated with slower eGFR decline $P<0.05$ (Table 3) (fig. 2). Calcium levels span from 6.2 to 10.3 mg/dL. Calcium levels initially and at follow up were not associated with progression.

The serum creatinine levels varied significantly among the groups in each month. ACR values differ significantly between patients where lower ACR significantly associated with slow progression. Regarding lipid profile, slow progression of kidney function was significantly associated with lower lipid profile parameters. In FBG levels, a significant difference in FBG values was found regarding slower CKD progression.

In terms of treatment received, a majority (84.0%) have been prescribed Alpha calciol, while 64.0% have been given phosphate binders. Cinacalcet has been administered to 5.0% of participants. The start of treatment was significantly associated with slower eGFR decline ($P<0.05$). The evolution of eGFR levels across 6 months after treatment initiation showed that eGFR increase across time points, with significant differences in eGFR across the six months (Table 4) (fig. 3).

**Table 1:** Clinical and biochemical characteristics of the patients:

| Characteristics | Whole patients (n= 200) |
|---|---|
| Demographics | |
| Age (years) mean±SD | 56.87±10.97 |
| Sex, male % | 42% |
| Physical examination | |
| BMI (Kg/m$^2$), mean±SD | 27±5.5 |
| SBP (mmHg), mean±SD | 140.5±20 |
| DBP (mmHg), mean±SD | 76±10 |
| Comorbidities | |
| Diabetic (%) | 40% |
| FBG (mg/dl) | 118.50±27.47 |
| Dyslipidemia (%) | 60% |
| Total cholesterol (mg/dl), mean±SD | 203.20±53.58 |
| HDL (mg/dl), mean±SD | 41.50±9.44 |
| LDL (mg/dl), mean±SD | 122.80±35.01 |
| TG (mg/dl) mean±SD | 161.30±43.99 |
| Blood chemistry | |
| Phoshpate (mg/dl), mean±SD | 4.56±1.03 |
| Calcium (mg/dl), mean±SD | 8.85±0.77 |
| Total ALP(U/L) median (Q1-Q3) | 76 (55-104) |
| PTH median (Q1-Q3) | 165 |
| Hemoglobin g/dl, mean±SD | 10.07±1.6 |
| Hs-CRP (mg/ml), median (Q1-Q3) | 2.5 (0.9-4) |
| Renal function | |
| CKD-EPI eGFR, ml/min/1.73m$^2$, mean±SD | 30.25±10.93 |
| Creatinine mg/dl, median (Q1-Q3) | 2.15 (1.7-2.98) |
| Urea mg/dl, median (Q1-Q3) | 68 (60-84) |
| Albuminuria, n(%) | |
| Normal | 33% |
| Microalbuminuria | 37% |
| Macroalbuminuria | 30% |
| CKD stage (n) % | |
| 3 | 100 (50%) |
| 4 | 100 (50%) |
| Treatment | |
| Phosphate binders n% | 64% |
| Alphacalcidol n% | 84% |
| Paricalcitol n% | 0% |
| Calcitriol n% | 0% |
| Cinacalcet n% | 5% |

BMI: body mass index , SBP: systolic blood pressure, DBP: diastolic blood pressure, ALP: alkaline phosphatase, FBG: fasting blood glucose, TG: triglycerides

**Table 2:** Evolution of serum phosphate levels in the three groups after therapeutic initiation.

| **Phosphate (mg/dL)** | **Initial** | **1st month** | **2nd month** | **3rd month** | **4th month** | **5th month** | **6th month** | **Test** | **p1** |
|---|---|---|---|---|---|---|---|---|---|
| **Group 1 (n = 84)** | | | | | | | | | |
| Mean±SD. | 3.48 ± 0.50 | 3.51 ± 0.52 | 3.52 ± 0.55 | 3.61 ± 0.60 | 3.59 ± 0.68 | 3.59 ± 0.71 | 3.57 ± 0.75 | Fr= 13.839* | 0.017 |
| Median | 3.00 | 3.30 | 3.20 | 3.70 | 3.60 | 3.30 | 3.50 | | |
| Min.-Max. | 2.68 – 4.0 | 2.80 – 4.40 | 2.84 – 4.50 | 2.88 – 5.0 | 2.90 – 5.60 | 2.95 – 5.80 | 3.0 – 6.0 | | |
| **p2** | | 0.187 | 0.606 | 0.187 | 0.496 | 0.757 | 0.037* | | |
| **p3** | | | 0.321 | 0.421 | 0.232 | 0.837 | 0.009* | | |
| **p4** | | | | | 0.045* | 0.312 | 0.001* | | |
| **Pairwise** | | | | | p5=0.322, p6=0.161, p7=0.017* | | | | |
| **Group 2 (n = 44)** | | | | | | | | | |
| Mean ± SD. | 5.80 ± 0.37 | 5.24 ± 0.35 | 5.08 ± 0.32 | 4.87 ± 0.33 | 4.67 ± 0.37 | 4.53 ± 0.37 | 4.33 ± 0.44 | Fr= 216.35* | <0.001* |
| Median | 5.60 | 5.30 | 5.10 | 4.90 | 4.70 | 4.58 | 4.40 | | |
| Min. - Max. | 4.90 – 5.58 | 4.70 – 5.80 | 4.50 – 5.50 | 4.20 – 5.38 | 4.0 – 5.32 | 3.80 – 5.26 | 3.60 – 5.20 | | |
| **p2** | | <0.001* | 0.012* | <0.001* | <0.001* | <0.001* | <0.001* | | |
| **p3** | | | 0.008* | 0.009* | <0.001* | <0.001* | <0.001* | | |
| **p4** | | | | | 0.009* | <0.001* | <0.001* | | |
| **Pairwise** | | | | | p5=0.053, p6<0.001*, p7=0.004* | | | | |
| **Group 3 (n = 72)** | | | | | | | | | |
| Mean ± SD. | 5.77 ± 0.50 | 5.36 ± 0.61 | 5.26 ± 0.48 | 5.07 ± 0.40 | 5.01 ± 0.33 | 4.89 ± 0.51 | 4.71 ± 0.64 | Fr= 82.77* | <0.001* |
| Median | 5.4 | 5.0 | 5.12 | 5.08 | 5.0 | 4.65 | 4.60 | | |
| Min. - Max. | 4.68 – 5.58 | 4.70 – 6.40 | 4.70 – 5.94 | 4.48 – 5.88 | 4.22 – 5.80 | 3.96 – 5.76 | 3.70 – 5.70 | | |
| **p2** | <0.001* | <0.001* | 0.548 | <0.001* | 0.001* | <0.001* | <0.001* | | |
| **p3** | | | 0.001* | 0.001* | 0.009* | <0.001* | <0.001* | | |
| **p4** | | | | | 0.449 | 0.275 | <0.001* | | |
| **Pairwise** | | | | | p5=0.065, p6<0.001*, p7=0.010* | | | | |

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, Fr: Freidman test,
p1: Comparing the different periods, p2: Comparing **1st month** and each other periods,
p3: Comparing **2nd month** and each other periods, p4: Comparing **3rd month** and each other periods,
p5: Comparing **4th month** and **5th month**, p6: Comparing **4th month** and **6th month**,
p7: Comparing **5th month** and **6th month**, *: Significant when p value <0.05.

**Table 3:** Evolution of PTH level in the three groups after therapeutic initiation.

| **PTH (pg./mL)** | **Initial** | **1st month** | **2nd month** | **3rd month** | **4th month** | **5th month** | **6th month** | **Test** | **p1** |
|---|---|---|---|---|---|---|---|---|---|
| **Group 1 n = 84** | | | | | | | | | |
| Mean ± SD. | 205±134.9 | 200.2±165 | 196.7±148.6 | 193±134.9 | 189.1±122.6 | 185.6±112.7 | 181.9±104.9 | Fr= 84.667* | <0.001* |
| Median | 187 | 160 | 180 | 168 | 156 | 144 | 133 | | |
| Min. - Max. | 126 – 970 | 120 – 1018 | 118 – 932 | 116 – 849 | 114 – 766 | 111 – 683 | 108 – 600 | | |
| **p2** | | 0.008* | 0.564 | 0.008* | <0.001* | <0.001* | <0.001* | | |
| **p3** | | | 0.029* | 0.039* | <0.001* | <0.001* | <0.001* | | |
| **p4** | | | | | 0.117 | 0.003* | <0.001* | | |
| **Pairwise** | | | | | p5=0.149, p6=0.001*, p7=0.070 | | | | |
| **Group 2 n = 44** | | | | | | | | | |
| Mean ± SD. | 85.97±19.16 | 85.23±20.34 | 84.82±18.20 | 84.77±18.16 | 84.86±17.07 | 85.57±18.82 | 87±18.98 | Fr= 0.966 | 0.965 |
| Median | 92 | 90 | 92 | 89 | 87 | 84.50 | 82 | | |
| Min. - Max. | 53 – 117 | 55 – 110 | 58 – 110 | 60 – 115 | 63 – 112 | 65 – 113 | 69 – 120 | | |
| **Group 3 n = 72** | | | | | | | | | |
| Mean ± SD. | 310.9±286.1 | 308±279.9 | 295±262.1 | 282.9±246.1 | 270.5±228.1 | 253.9±211.6 | 243.1±194.8 | Fr= 31.019* | <0.001* |
| Median | 197 | 196 | 184 | 187 | 190 | 176 | 172.5 | | |
| Min. - Max. | 135 – 1020 | 127 – 1100 | 123 – 1030 | 119 – 990 | 114 – 940 | 109 – 890 | 105 – 840 | | |
| **p2** | 0.030* | | 0.145 | 0.030* | 0.001* | <0.001* | <0.001* | | |
| **p3** | 0.473 | | | 0.473 | 0.066 | 0.022* | 0.001* | | |
| **p4** | | | | | 0.262 | 0.116 | 0.006* | | |
| **Pairwise** | | | | | p5=0.654, p6=0.102, p7=0.235 | | | | |

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, Fr: Freidman test,
p1: Comparing the different periods, p2: Comparing **1st month** and each other periods,
p3: Comparing **2nd month** and each other periods, p4: Comparing **3rd month** and each other periods, p5: Comparing **4th month** and **5th month**, p6: Comparing **4th month** and **6th month**,
p7: Comparing **5th month** and **6th month**, *: Significant when p value <0.05.

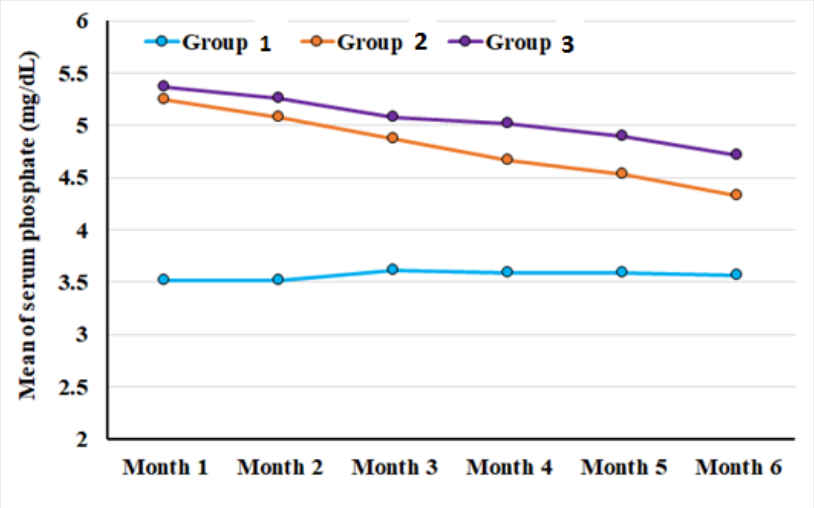


**Figure 1:** Evolution of serum phosphate levels in the three groups after therapeutic initiation.

**Table 4:** Evolution of eGFR after therapeutic initiation among each group.

| eGFR | Initial | 1st month | 2nd month | 3rd month | 4th month | 5th month | 6th month | Test | p1 |
|---|---|---|---|---|---|---|---|---|---|
| **Group 1 n = 84** | | | | | | | | | |
| Mean ± SD. | 32.79 ±10.38 | 32.73± 11.19 | 33.43±10.19 | 31.25±8.97 | 31.80±10.07 | 30.54±11.41 | 32.88±13.17 | Fr= 45.593 | <0.001* |
| Median | 35.0 | 34.0 | 35.0 | 31.0 | 31.0 | 26.0 | 31.0 | | |
| Min. - Max. | 15.0– 49.0 | 13.0 – 44.0 | 14.0 – 45.0 | 14.0 – 44.0 | 13.0 – 48.0 | 12.0 – 52.0 | 11.0 – 57.0 | | |
| **Group 2 n = 44** | | | | | | | | | |
| Mean ± SD. | 28.75 ±16.01 | 28.71± 16.71 | 29.41±15.71 | 30.27±15.86 | 31.36±16.04 | 32.68±16.26 | 34.82±17.05 | Fr= 39.225* | <0.001* |
| Median | 22.0 | 21.0 | 22.0 | 22.0 | 23.0 | 25.0 | 28.0 | | |
| Min. - Max. | 15.0 – 54.0 | 15.0 – 54.0 | 16.0 – 54.0 | 15.0 – 55.0 | 14.0 – 56.0 | 13.0 – 57.0 | 12.0 – 59.0 | | |
| **p2** | | 0.642 | 0.842 | 0.038* | 0.004* | <0.001* | <0.001* | | |
| **p3** | | | | 0.060 | 0.007* | 0.001* | <0.001* | | |
| **p4** | | | | | 0.425 | 0.154 | 0.003* | | |
| **Pairwise** | | | | | p5=0.531, p6=0.033*, p7=0.131 | | | | |
| **Group 3 n = 72** | | | | | | | | | |
| Mean ± SD. | 28.21 ±6.34 | 27.54± 6.48 | 28.54±7.48 | 27.15±8.72 | 27.08±11.37 | 26.47±12.62 | 25.88±14.56 | Fr= 61.174* | <0.001* |
| Median | 32.0 | 31.0 | 32.0 | 25.0 | 20.50 | 19.0 | 19.0 | | |
| Min. - Max. | 15.0 – 36.0 | 14.0 – 36.0 | 15.0 – 38.0 | 11.0 – 38.0 | 10.0 – 45.0 | 9.0 – 48.0 | 8.0 – 53.0 | | |
| **p2** | | 0.081 | 0.091 | 0.410 | 0.071 | <0.001* | <0.001* | | |
| **p3** | | | | 0.012* | <0.001* | <0.001* | <0.001* | | |
| **p4** | | | | | 0.327 | 0.003* | <0.001* | | |
| **Pairwise** | | | | | p5=0.045*, p6=0.002*, p7=0.285 | | | | |

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, Fr: Freidman test,
p1: Comparing the different periods, p2: Comparing **1st month** and each other periods,
p3: Comparing **2nd month** and each other periods, p4: Comparing **3rd month** and each other periods,
p5: Comparing **4th month** and **5th month**, p6: Comparing **4th month** and **6th month**,
p7: Comparing **5th month** and **6th month**, *: Significant when p value <0.05.

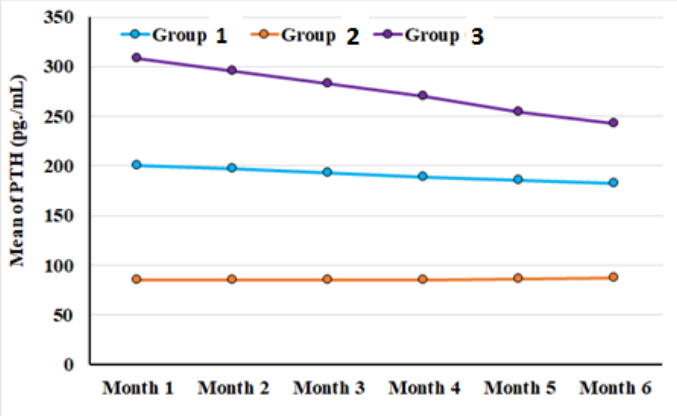


**Figure 2:** Evolution of PTH level in the three groups after therapeutic initiation.

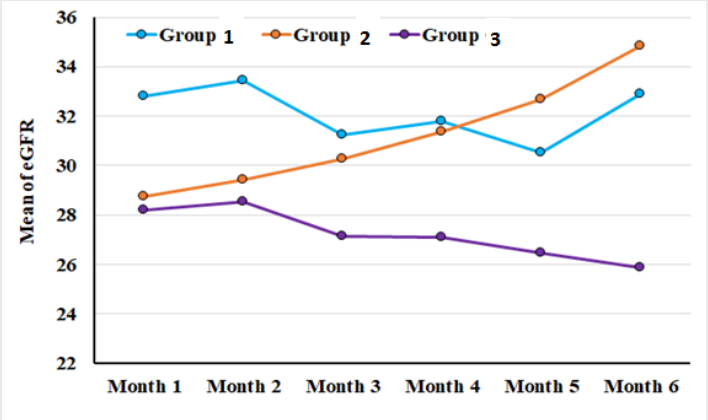


**Figure 3:** Evolution of eGFR in the three groups after therapeutic initiation.

## Discussion

Chronic Kidney Disease (CKD) is a progressive disease depending on many risk factors. Treatment of CKD aims at slowing progression as long as possible with better quality of life. Hyperphosphatemia and secondary hyperparathyroidism (SHPT) are major complications of CKD. They have been associated with higher morbidity and mortality.

We aim to assess the effect of control of secondary hyperparathyroidism (SHPT) and hyperphosphatemia on CKD progression in CKD stages 3 and 4, through a longitudinal follow up approach based on repeated measurements of variables.

Regarding the demographic variables between patients, neither age nor sex showed significant difference in between groups, which shows an overall balance in the demographic characteristics between the studied groups. The statistical analysis showed no significant differences on slow or rapid CKD progression regarding age and gender. In parallel to the present study, Magagnoli et al., showed that age and sex didn't affect the relation between CKD-MBD biomarkers and mortality [22].

Regarding the initially measured eGFR of patients, it was found that the higher eGFR the better the result, and that CKD progression was more in advanced stage (stage 4 more than stage 3), this comes in line with Bozic et al. in their NEFRONA cohort study. This emphasizes the importance of early management of CKD-MBD starting from stage 3a as recommended by guidelines [23].

Serum calcium abnormalities are from the early changes of CKD-MBD, in the present study no association was found between serum calcium level and progression of CKD. In consistency with our findings, Magagnoli et al., found that no relation between calcium levels and mortality, while there is a significant interaction between calcium and phosphate level showing that hypercalcemia is associated with a higher mortality risk in combination with hyperphosphatemia [22].

However recent guidelines recommend avoidance of both hypercalcemia and hypocalcaemia with individualized treatment plan for each patient to avoid hazards of treatment.

Phosphate is considered a key role player in CKD-MBD derangement. Various studies have proven an association between phosphate and higher CV and non CV mortality ([22]). Bellasi et al., found that high baseline phosphate levels in CKD patients >4.3 mg/dl had higher mortality risk than those with phosphate level 3.3-3.8 mg/dl by about 49% [24]. Furthermore, Kestenbaum et al. confirmed that any 1mg/dl increase in serum phosphate is associated with 33% higher risk of mortality in different CKD

stages[25] .Our results further strengthen these previous studies as statistical analysis showed that the lower phosphate level at baseline and follow up records the slower was the progression.

Several studies have linked secondary hyperparathyroidism (SHPT) to a higher morbidity and mortality of CKD patient [26]. SHPT is associated with cardiovascular complications and risk of cardiovascular events [27,23]. Our results further strengthen these findings and confirm them. It was found that lower PTH levels are significantly associated with slower progression.

The study showed that receiving treatment either phosphate binders, α-calcidol or cinacalcet for CKD-MBD abnormalities is significantly associated with slower progression. This comes in agreement with many authors recommending the start of specific secondary hyperparathyroidism (SHPT) and hyperphosphatemia treatment as early as stage 3 CKD [12].

Many studies have proven the role of calcium sensing receptors i.e. cinacalcet in the delay of CKD progression and CVS complications [28,29]. Tossaint et al., discussed the benefits of use of vitamin D receptor activators (VDRAs) to control secondary hyperparathyroidism (SHPT) in CKD stages 3-5 and emphasized putting in mind the harms of treatment as hypercalcemia and recommended furthermore studies to discuss their use in moderate CKD stages [30].

Regarding other risk factors of CKD progression, at enrollment all patients were in stable clinical condition, and none had intercurrent infections or acute inflammatory processes. Blood pressure measurements of the studied patients were on average 140.5±20/76±10 mmHg. Diabetes mellitus (DM) is considered an established risk factor for CKD progression. Our results showed association between disease progression, glucose levels, and DM among the studied patients. Patients with slow progression exhibited lower FBG levels, with a significant difference in FBG values between those with and without slow progression. In parallel to these findings, Jung et al showed that a fasting blood glucose level of 126 mg/dL to less than 160 mg/dL was associated with decreased risk of the composite outcome of serum creatinine doubling, end-stage kidney disease, or death from chronic kidney disease [31].

The strengths of this study include the longitudinal follow up manner, and that we didn't depend on a single baseline measurement only as most of the previous studies. In addition the classification of population into small subgroups allowed testing the independent effect of each parameter. Most of the previous studies focused on CKD-MBD parameters and derangement squeal, but we focused on the result of their control.

Drawbacks include the relatively small sample size, short follow up time and that the cases are localized in one town limits the results' generalization. More wide national and international studies are needed. Results can be confirmed with longer follow up period studies. The new up-to-date drugs are still not widely used, which made us miss the chance of testing their effect on CKD progression.

## Conclusion

In conclusion, our cohort study in stage 3 and 4 CKD patients showed that the control of secondary hyperparathyroidism (SHPT) and hyperphosphatemia are independently associated with slowing chronic kidney disease progression, which encourages interventions at different levels of MBD to delay loss of renal function in this population.

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