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# Association between Ca, P & Mg in non-hospitalized chronic renal failure patients

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**ABSTRACT**

Alterations in mineral metabolism has been observed in all patients suffering from kidney disorders. While elevations in urea and creatinine values are definitely suggestive of renal disease, alterations in minerals metabolism is a secondary findings in all such cases. The metabolism of major macro divalent metals calcium and magnesium along with phosphorus are altered significantly and elevation in the level of one of the analytes always decreases the other. In the past, numerous publications have been carried out in this field, but only very few studies have been done to find out the associations between the analytes. This paper present the clinical usefulness of measuring all three analytes in patients suffering from kidney related disorders.



## Introduction

Abnormalities of mineral metabolism occur earlyin chronic kidney disease. Quantification of the prevalence of these abnormalities has not been described using current assays nor in large unselected populations.Calcium, phosphate and magnesium are present abundantly in human body and its disturbance usually occurin people who have had kidney function down to less than 40% of normal. More rarely, Calcium and phosphate problems can occur in people with other kidney diseases. A fall in the blood level of calcium is the first major change. As the kidneys do not convert vitamin D into its active form, calcium does not get into the body from food, and the blood level of calcium can fall. Levels of phosphate in the blood will rise, because the kidneys are not excreting excess phosphate into the urine. Calcium and phosphate metabolism are disturbed in moderate to severe CKD, and marked disturbances in either should usually lead to referral for detailed assessment. Phosphorus, an element found in most foods, also helps to regulate calcium levels in the bones. In Kidney dysfunction, phosphorus levels in the blood will raise leading to lower levels of calcium in the blood resulting in higher PTH levels together with loss of calcium from the bones. Magnesium, the fourth most abundant cation in the body, plays an important role in numerous enzymatic reactions, transport processes and synthesis of proteins, DNA and RNA. In contrast to its physiological role, the clinical importance of magnesium is often underestimated. Furthermore serum magnesium concentrations are not measured routinely in hospitalized patients and thus most magnesium abnormalities are remaining undetected Moderate hypermagnesaemia, however, seems to have beneficial effects on vascular calcification and mortality rates in CKD patients. On the other hand, higher serum magnesium levels are reported to be linked to lower PTH levels and results on the effects on bone are controversial. In addition, low magnesium levels are associated with low bone mass, osteoporosis and vascular calcification. Hence a definite relationship between the three analytes will help nephrologists in treating such patients by dialysis.

## Literature Review

Studies on the metabolic profile of many cells have shown that chronic renal failure (CRF) is associated with a significant elevation in the basal levels of cytosolic calcium (Ca). This latter abnormality is, in major part, responsible for the organ dysfunction in CRF. Prevention of secondary hyperparathyroidism in CRF or blocking of the effect of Parathyroid Hormone (PTH) by a calcium channel blocker results in normalization of Ca and restoration of cell function. Thus, the available data are consistent with the notion that CRF is a state of cellular Ca toxicity, which underlies many of the metabolic and functional derangements in CRF.(1)

Hyperparathyroidism in incipient renal failure occurs at normal serum phosphate and Ca values. Hyperparathyroidism, is already present in a sizable proportion of patients with moderate a Glomerular Filtration Rate (GFR) of 60–90 mL/min. Decreased $1,25(OH)_3D$ values in very early renal failure, despite elevated intact PTH, points to abnormal regulation of biosynthesis of $1,25(OH)_2D3$. Abnormal regulation of vitamin D metabolismoccurs early in CRF.(2)Low doses of calcitriol plus calcium carbonate seem to improve the biochemical and bone derangements in early renal failure.(3)Control of serum phosphorus (P) levels is a central goal of managing patients with CRF. Hyperphosphatemia develops invariably with kidney failure, and inadequate control of serum P leads to an elevated Ca × P product. Elevated P and Ca × P product are both significant predictors of cardiovascular mortality in hemodialysis patients. These effects are observed at P and Ca × P product levels that were considered safe until recently. Based on current national studies,serum P levels and Ca × P product of patients with CRF be maintained between 3.0 -- 5.0 mg/dL and less than 55 $mg^2/dL$, respectively.(4)

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Elevated serum P is a predictable accompaniment of end-stage renal disease (ESRD) in the absence of dietary phosphate restriction or supplemental phosphate binders. For hemodialysis patients who have been receiving dialysis for at least 1 year, a large percentage of patients have a serum P level above 6.5 mg/dL and that this places them at increased risk of death. This increased risk is independent of PTH. The mechanism(s) responsible for death is unknown, but may be related to an abnormally high Ca x P product. Although mechanisms are not clearly established, there is need for vigorous control of hyperphosphatemia to improve patient survival.[5]More efficient P binding permits serum P concentration to be controlled with lower doses of Ca salts. The higher P binding/Ca absorption ratio coupled with a lower dose indicates that less Ca will be absorbed when calcium acetate is used for P control. Markedly positive Ca balance, hypercalcemia and ectopic calcification should be less likely to occur with this drug than other calcium salts.[6]Recent in vitro and in vivo studies have shown that calcium acetate (CaAC) is a more effective than calcium carbonate ($CaCO_3$). More efficient binding allows serum P to be controlled with a lower dose; moreover, less Ca seems to be absorbed when CaAC is used. [7]

Since CaAC binds twice as much phosphate for the same dose of elemental calcium as CaCO3, its use has been recommended. However, clinical experience has shown that in spite of the fact that half the dose of Ca element given as acetate does actually control predialysis plasma phosphate as well as Ca and the incidence of hypercalcemia is not decreased, probably because Ca availability at the alkaline pH of the intestine is much greater with Ca AC. When hypercalcemia is frequent (and not explained by autonomized hyperparathyroidism, adynamic bone disease, overtreatment with vitamin D, granulomatosis or neoplasia) it is necessary either to decrease the dose of Ca and complete the necessary binding of P by adding small doses of $Mg(OH)^2$ or magnesium carbonate, provided that dialysate Mg is decreased to 0.48 -0.7mg/dL to prevent hypermagnesemia or to decrease the dialysate Ca(DCa) concentration. The decrease of DCa can be made either just when hypercalcemia occurs or on a systemic basis according to the amount of CaCO3 used and to the necessity of associating 1 alpha(OH) vitamin D3 derivatives.[8]It is recommended to adjust albumin levels in the event of hypoalbuminemia (for each g/dL of decrease in albumin, total serum Ca decreases by 0.9 mg/dL). The following formula facilitates rapid calculation of corrected total Ca: Corrected total Ca (mg/dL) = measuredCa (mg/dL) + 0.8 [4-albumin (g/dL)]. PTH and "Intact" PTH are the biochemical parameters that best correlates with bone histology levels measured when serum Ca and P levels are adequately controlled.[9]

Widespread use of Ca-based phosphorus binders has evidenced the frequent appearance of hypercalcaemia and long-term progressive cardiovascular calcification. Sevelamer, a relatively new phosphorus binder, has proved efficacious in lowering serum P and PTH levels without inducing hypercalcaemia. Patients with low normal levels of Ca may receive Ca-based phosphorus binders with little risk. Patients with low values of PTH and high normal Ca should receive Sevelamer. Tailored combinations of Ca-based phosphorus binders and Sevelamer should be considered, and DCa concentration adjusted accordingly.[10]A suitable DCa concentration is important and must take into consideration the medical therapy and the Ca balance on an individual patient basis. Surgical parathyroidectomy is the ultimate means of treating hypercalcaemic hyperparathyroidism, when medical therapy has failed. Achieving an evidence-based consensus can give clinicians a useful tool for the treatment of disturbances of Ca-P metabolism in chronic renal insufficiencyand this has become an important objective in nephrological care, particularly as ageing and increased risk of atherosclerosis have become major issues in the dialysis population.[11]

Patients with low values of PTH and high normal Ca should receive Sevelamer. Tailored combinations of Ca-based phosphorus binders and Sevelamer should be considered, and Ca dialysate concentration adjusted accordingly.[12]Elevated serum P levels have been linked to vascular calcification and mortality among dialysis patients. The relationship between P and mortality has not been explored among patients with CKD. In a retrospective cohort study from eight Veterans Affairs' Medical Centers located in the Pacific Northwest, CKD was defined by two continuously abnormal outpatient serum creatinine measurements at least 6 months apart. Mortality risk increased linearly with each subsequent 0.5-mg/dL increase in serum P levels. Elevated serum P levels were independently associated with increased mortality risk among the population of patients with CKD.[13]Paricalcitol in CKD patients was associated with modest increases in Ca and P levels. Paricalcitol reduces bone specific alkaline phosphatase levels, which may be beneficial for reducing vascular calcification.[14]Low-grade albuminuria (LGA) was demonstrated to be related to increased cardiovascular events in various study populations. Higher serum P was independently related to LGA in individuals without evidence of renal dysfunction. Further investigations are warranted to clarify the precise mechanism of the association between serum P and LGA.[15]

24-hour proteinuria reduced modestly in patients who maintained relatively higher serum P levels or relatively higher phosphaturia to be maximal in those who achieved the lowest level of serum and urine P. P is an important modifier of the anti-proteinuric response to very low protein diet. Reducing phosphate burden may decrease proteinuria and slow the progression of renal disease in CKD patients, an issue that remains to be tested in specific clinical trials.[16]Patients with ESRD who had a reduced rate of Ca absorption (presumably due to deficiency of 1,25-dihydroxycholecalciferol) were found to have a severe depression of Mg absorption. On the other hand, patients with absorptive hypercalciuria and nephrolithiasis, who had an increased rate of Ca absorption, were found to absorb Mg normally. These results suggest that Mg absorption in the human is mediated by a transport process different from that which facilitates Ca absorption, and that normal Mg absorption may be dependent on vitamin D.[17]

Renal excretion is the major route of Mg elimination from the body and a positive Mg balance would be expected under conditions of renal insufficiency. However, a compensatory decrease in tubular reabsorption is operating to maintain an adequate urinary Mg excretion even when glomerular filtration rates are very low. Nevertheless, in ESRD patients, the limited ability of the kidney to excrete an increased Mg load may result in toxic ionic concentrations of the ion in serum. While Mg intoxication is a real hazard when Mg-containing drugs are given, Mg balance may be normal or even decreased in uraemic patients. This is usually due to decreased dietary intake combined with the impaired intestinal Mg absorption which characterizes CRF. Impairment of Mg absorption seems to be related to deficient synthesis of the active metabolite of vitamin D by the non-functioning kidney. Following the institution of chronic haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) treatment, the major determinant of Mg

balance is the concentration of Mg in the dialysate. Changes in the dialysate Mg have been used to reduce the incidence of renal osteodystrophy, to alleviate uraemic pruritus, or to retard the development of arterial calcification in chronic renal disease. However, uncertainty about Mg, Ca and PTH relationships in renal failure makes a reasoned approach to such manipulations extremely difficult.(18)

Patients on chronic CAPD program during several months had normal calcemia, phosphatemia and normal alkaline phosphatase, and that they had Ca x P product in the recommended range, and serum PTH level ranged from 16 to 490 pg/L. A balanced diet and a correct dosage of phosphate binders, as well as a careful substitution with active vitamin D metabolites render a good control of serum Ca and P balance, as well as an effective prevention of renal osteodystrophy development in the patients on chronic peritoneal dialysis treatment.(19)

Skeletal-muscle Mg, estimated as an index of body Mg store, was significantly lower (p less than 0.05) in advanced CRF (most of whom showed hypermagnesemia) than in controls matched for sex and age. There is indirect evidence that renal insufficiency sets at a new level forthe control of Mg gradient across the cell membrane.Depletion of total-body Mg was probably due to inadequate intake, as supplied by the modified Giovannetti diet, and impaired absorption, exacerbated by frequent vomiting. Peritoneal dialysis did not contribute greatly to Mg depletion in the patients.(20)Low Mg levels have been associated with impairment of myocardial contractility, intradialytic hemodynamic instability, and hypotension. In addition, low Mg has been also linked to carotid intima-media thickness, a marker of atherosclerotic vascular disease and a predictor of vascular events.(21)Increasing evidence points towards a link between Mg and CVD, even in subjects without CKD.(22)$MgCO_3$ administered for a period of 6 months is an effective and inexpensive agent to control serum P levels in hemodialysis patients. The administration of $MgCO_3$ in combination with a low dialysate Mg concentration avoids the risk of severe hypermagnesemia.(23)

Factors affecting serum Mg concentrations in hemodialysis patients, such as dietary Mg intake, should be investigated in more detail. Through further extended studies, the current dialysate Mg concentration (1.0 mmol/L used in most countries), one of the strong contributors to the serum Mg concentrations of hemodialysis patients, might be reconsidered for the better survival of hemodialysis patients. (24)

Data provided by recent studies on these issues have promoted promising renewed interest in the role of Mg in ESRD and its possible favorable therapeutic application in these patients. Further large studies are needed to establish its efficacy and safety, and, probably, to re-evaluate its appropriate concentration in hemodialysis and CAPDfluids.(25) Intradialyticchanges in serum Mg have no correlation with intradialytic changes in serum Ca or with PTH level. However, it was significantly correlated with hypotension during the dialysis session, especially with acetate dialysate. Further investigations are needed to determine whether or not this is true in patients using bicarbonate dialysis.(26) A study revealed a high prevalence of hypophosphatemia among CAPD patients as well as a defect in renal phosphate reabsorption secondary, at least in part, to pharmacologic therapy. Moreover, it also suggests that in CAPD patients muscle P content is likely to be reduced in presence of hypophosphatemia. (27)

**Materials and methods**

After thorough fully going through the literature review, in connection with the project topic, a reasonable number of 50 non hospitalized patients attending nephrologyclinic and whose serum creatinine levels >5 mg/dLwere selected for this study. This consisted of both males and female in the age group of 21 to 79 years.

As the sole aim of this study is to compare the association between Ca, P, Mg levels in CRF patients Inclusion or exclusion criteria were not followed. Olympus AU400 analyser was used to measure these analytes. Calcium was measured using Arsenazo III dye binding, Magnesium using xylidyl blue dye binding and phosphorus by UV kinetic.

**Statistical Analysis**

For statistical analysis of data, a software downloaded from the website http://www.vassarstats.net was used to calculate correlation coefficient (r), students 't' distribution (t) and probability (p) between two analytes to compare the association between them.

**Results**

The results and the statistical parameters obtained for the analytes studies are presented in Table I to IV.

Table I presents the mean results obtained for the analytes measured and the ratios obtained between the analytes. This Table contains data for all patients as wellas males &females. The normal values used in the author's laboratory are also presented in this Table for comparison. The mean value for calcium for all group of patients are at the lower end of normal range, bothP and Mg are well within the normal range indicating hypocalcemia is prevalent in CRF patients. Similarly both Ca/P and Ca/Mg ratios are higher and is more pronounced in the later.Table II, III & IV shows statistical data( r, tand p) obtained for all patients and males & females. These data shows the probability obtained between two pairs of analytes compared. Very good correlations were observed in all comparisons and in all groups of patients suggesting that the chosen analytes in renal failure patients are indeed shows association among themselves.

**Discussion**

Metabolic alterations of Ca, P and Mg have been well established and regulating their levels during dialysis in patients identified of having CRF and ESRD have been highlighted in many previous studies (7,9). Elevated P and decreased Ca in serum is observed in a majority of studies and our findings are in consistent with previous studies (9,15). This study to interlink Ca, P and Mg was due to earlier observations in the alteration of these analytes metabolism(7,11,15). While most of the previous studies have predicted the levels of these analytes in ESRD patients, studies linking the association between any two analytes are sparse. Measuring these three analytes aremandatory to supplement the diagnosis of CRF and ESRD. Such studies in pre and post dialysis patients may throw some light on the usefulness of using Ca, P andMg supplementation in the dialysate fluids.

**Conclusion**

This study established that Ca, P and Mg are indeed associated with each other, making them as clinically useful investigations in the diagnosis of renal dysfunctions. These tests should be included as package tests along with urea and creatinine as the primary renal package I test. Measurements of these analytes may help to decide supplementation of these analytes in the dialysate fluid. However, this is not feasible because majority of hospitals doing dialysis uses concentrate dialysate fluid supplied by companies.

**Table I . Mean values for Ca , P & Mg (All patients)**

| S.No | All groups | | | Ca | P | Mg | Ca/P | Ca/Mg | P/Mg |
|---|---|---|---|---|---|---|---|---|---|
| 1 | CRF (n=50) | All (n=50) | Mean | 8.42 | 4.44 | 2.09 | 1.9 | 4.02 | 2.12 |
| | | Male (n=35) | Mean | 8.5 | 4.3 | 2.1 | 1.9 | 4.05 | 2.05 |
| | | Female (n=15) | Mean | 8.2 | 4.8 | 2.1 | 1.7 | 3.9 | 2.28 |
| 2 | Normal Range | | | 8.4 - 10.2 | 2.8 – 5.9 | 1.6 – 2.3 | 2.2 | 4.76 | 2.12 |

**TABLE II. Statistical Data for all patients (n=50)**

| S.No | Analytes compared | r-value | t-value | p-value |
|---|---|---|---|---|
| 1 | CaVs P | -0.246 | -1.758 | <0.05 |
| 2 | CaVsCa/P | 0.33 | 2.422 | <0.01 |
| 3 | CaVsCa/Mg | 0.41 | 3.114 | <0.01 |
| 4 | CaVs P/Mg | -0.38 | -2.846 | <0.01 |
| 5 | P Vs Mg | 0.38 | 2.846 | <0.01 |
| 6 | P VsCa/P | -0.78 | -8.636 | <0.000001 |
| 7 | P VsCa/Mg | -0.39 | -2.934 | <0.01 |
| 8 | P Vs P/Mg | 0.77 | 8.361 | <0.000001 |
| 9 | Mg VsCa/Mg | -0.83 | -10.31 | <0.000001 |
| 10 | Mg Vs P/Mg | -0.24 | -1.713 | <0.05 |
| 11 | Ca/P VsCa/Mg | 0.29 | 2.099 | <0.05 |
| 12 | Ca/P Vs P/Mg | -0.71 | -6.985 | <0.000001 |

**TABLE III. Statistical Data for Male patients (n=35)**

| S.No | Analytes compared | r-value | t-value | p-value |
|---|---|---|---|---|
| 1 | CaVs P | -0.402 | -2.522 | <0.01 |
| 2 | CaVsCa/P | 0.341 | 2.08 | <0.01 |
| 3 | CaVsCa/Mg | 0.492 | 3.246 | <0.01 |
| 4 | CaVs P/Mg | -0.454 | -2.927 | <0.01 |
| 5 | P VsCa/P | -0.840 | -8.893 | <0.000001 |
| 6 | P VsCa/Mg | -0.366 | -2.26 | <0.05 |
| 7 | P Vs P/Mg | 0.793 | 7.48 | <0.000001 |
| 8 | Mg VsCa/Mg | -0.826 | -8.418 | <0.000001 |
| 9 | Mg Vs P/Mg | -0.339 | -2.07 | <0.05 |

**TABLE IV. Statistical Data for Female patients (n=15)**

| S.No | Analytes compared | r-value | t-value | p-value |
|---|---|---|---|---|
| 1 | P Vs Mg | 0.576 | 2.541 | <0.05 |
| 2 | P VsCa/P | -0.721 | -3.752 | <0.01 |
| 3 | P VsCa/Mg | -0.461 | 1.873 | <0.05 |
| 4 | P Vs P/Mg | 0.771 | 4.365 | <0.000001 |
| 5 | Mg VsCa/Mg | -0.868 | -6.303 | <0.000001 |
| 6 | Ca/P Vs P/Mg | -0.706 | -3.594 | <0.01 |

Many data from more studies when published will make awareness to the company to adjust suitably the levels of these analytes so as to make the levels normal after each dialysis session.

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