Control of calcium-phosphorus metabolism in hemodialysis and its adaptation to K/DOQI 2003 guidelines

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SUMMARY

Backgroung: *The publication in 2003 of the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommended targets levels for serum iPTH, Ca, P, and CaxP product. However, many patients do not achieved these target ranges. It is necessary to known the percentage of patients out of range in order to prevent the development of bone disease and to reduce mortality and morbidity.*

Objectives: *To know the degree of control of of Ca-P metabolism in haemodialysis patients in our haemodilalysis facilities and the achievement of target levels recommended by K/DOQI Guidelines.*

Patients and methods: *We have retrospectively investigated in 190 prevalent haemodialysis patients (males 58,2%, ratio M/F 1,4, mean age 70 years, range 17-87 years, at least 3 month in haemodialysis) the serum levels of Ca, albumin-corrected serum Ca, P, CaxP product and iPTH in all analitycal determinations performed in 2004. In each patient we have obtained the average (and median) of these serum markers. Cut-off levels were carried out following the recommendations of the K/DOQI Guidelines.*

Results: *The average of serum Ca and albumin-corrected serum Ca is normal (means ± SD = 8,9 ± 0,6 mg/dL and 9,2 ± 0,7 mg/dL, respectively); however, 53,7% has normal values, 9,1% hypocalcemia and 37,1% hypercalcemia. The average of serum P is also normal (mean ± SD = 5,0 ± 1,3 mg/dL); however, only 57,17% has normal values, and 11,7% has hypophosphoremia and the remaining 31,1% hyperphosphoremia. The CaxP product is normal (mean ± SD = 46,3 ± 13,3 mg^2/mL^2), 4,9% with low values and 23,4% with high values. The median of serum iPTH is 253 pg/mL, but only 31,1% of them have normal values, 25,1% low range values and 43,7% has hyperparathyroidism; 9,3% with iPTH higher than 800 pg/mL. The percentage of patients with hyperphosphoremia is higher in the group with iPTH higher than 300 pg/mL (23,3% vs 40%, chi^2, p= 0,006). In patients with PTHi in normal range, 3,6% have low CaxP product and the remaining 17,8% high CaxP product. Overall, only 25% of patients falls within recommended ranges for all indicators of mineral metabolism and 17% has all serum markers outside these recommendations.*

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Conclusions: *The degree of control of mineral metabolism in haemodyalisis patients if clearly insufficient and a large percentage of them do not achieved the recommended serum targets recommended by K/DOQI Guidelines. This groups of patients are exposed to a increased risk for oseous and cardiovascular morbimortality. Tha analysis of adequancy must be performed with percentage of patients out of range in order to apply new therapeutical strategies.*

Key words: ***Calcium. Phosphorus. iPTH. K/DOQI Guidelines.***

CONTROL DEL METABOLISMO CALCIO-FOSFORO EN HEMODIALISIS Y SU ADECUACION A LAS GUIAS K/DOQI 2003

RESUMEN

Introducción: *Desde la publicación de las Guías K/DOQI en 2003 sobre metabolismo mineral en la enfermedad renal crónica se ha observado que algunos pacientes no alcanzan en la práctica clínica un adecuado control y es necesario conocer el porcentaje de ellos que están fuera de rango normal, para evitar complicaciones metabólicas y cardiovasculares.*

Objetivos: *Conocer el grado de control del metabolismo Ca-P en pacientes tratados con hemodiálisis en nuestra provincia, estudiando los valores de tendencia central y el porcentaje de casos que se encuentran dentro y fuera de rango.*

Pacientes y métodos: *Estudio retrospectivo realizado en 190 pacientes (58,2% varones, V/H 1,4, mediana de edad 70 años, rango de edad 17-87 años) incluidos en hemodiálisis durante al menos 3 meses, durante todo el año 2004. De cada paciente se obtiene la media (o mediana) de los valores de Ca, Ca corregido con albúmina, P, producto CaxP y PTHi. Los niveles de corte se establecen según las recomendaciones de las Guías K/DOQI de 2003.*

Resultados: *Las medias de Ca total y corregido con albúmina están en rango normal (medias ± DE = 8,9 ± 0,6 mg/dL y 9,2 ± 0,7 mg/dL, respectivamente); no obstante el 53,7% de ellos tienen valores de normocalcemia, mientras que el 9,1% tiene hipocalcemia y el 37,1% hipercalcemia. La media de P también se encuentra en rango normal (media ± DE = 5,0 ± 1,3 mg/dL); no obstante sólo el 57,1% de ellos tienen valores en rango normal, mientras que el 11,7% tiene hipofosforemia y el 31,1% hiperfosforemia. El producto CaxP se encuentra en rango normal (media ± DE = 46,3 ± 13,3 mg^2/mL^2, pero un 4,9% tiene valores disminuidos y un 23,4% valores elevados. La mediana de PTHi es 253 pg/mL, pero sólo el 31,1% se encuentra en el rango normal mientras que el 25,1% tiene valores disminuidos y un 43,7% en rango de hiperparatiroidismo, entre ellos un 9,3% con niveles por encima de 800 pg/mL. El porcentaje de casos con hiperfosforemia es superior en el grupo de pacientes con niveles de PTHi superiores a 300 pg/mL (23,3% vs 40%, chi^2, p = 0,006). Entre los pacientes con valores de PTHi en rango normal, un 78,6% tienen un producto CaxP normal, un 3,6% disminuido y el 17,8% restante elevado. Al analizar los resultados globales, sólo la cuarta parte de los pacientes presenta un perfil completo en rango normal y un 17% tiene todos los parámetros fuera de rango.*

Conclusiones: *El control del metabolismo Ca-P es insuficiente y muchos pacientes no se encuentran en los rangos recomendados por las Guías K/DOQI de 2003, por lo que están expuestos un mayor riesgo de complicaciones óseas y cardiovasculares. El análisis de la adecuación de los parámetros del metabolismo Calcio-Fósforo a las debe realizarse mediante porcentajes para conocer el grupo de pacientes que requieren nuevas estrategias terapéuticas.*

Palabras clave: ***Calcio. Fósforo. PTHi. Guías K/DOQI.***

INTRODUCTION

Calcium-phosphorus (Ca-P) metabolism impairments in patients with chronic renal disease are associated not only with musculoskeletal impairments but also with an increased risk of cardiovascular morbidity and mortality. The publication of K/DOQI guidelines in 2003 on mineral metabolism[1] has established a range of «normal» values for serum Ca and P levels, for Ca (P product and for iPTH (Table I), out of which the risk of the above mentioned complications increases. The complexity of Ca-P metabolism pathophysiology and limitations of current therapies make control of these changes being a clinical challenge and a source of frustration in clinical practice. In fact, most of dialysis patients are not well controlled.[2-4]

In this work, we review the degree of control of Ca-P metabolism in patients on hemodialysis in our province (Ciudad Real) by studying central tendency values and the percentage of cases that are in and out of the range established by K/DOQI 2003 guidelines.

PATIENTS AND METHODS

This is a retrospective study performed on 190 patients included in the hemodialysis program for at least 3 months, during all year 2004, 116 at the Hospital Unit, and 74 at two contracted centers (43 patients at Nuestra Sra del Prado of Ciudad Real and 31 patients at Centro Asyter of Puertollano). Median age was 70 years (with no normal distribution), with age range of 17-87 years, 58.2% males, with a M/F ratio of 1.4. A mean value is obtained for each patient for the following parameters: Ca, albumin-corrected Ca (Ca-albumin+4), P, Ca (P, and iPTH, independently of the number of determinations done throughout 2004. Then, the central trend value is calculated (mean, median) for each one of the indicated parameters.

Table I. Goals for controlling bone metabolism markers in stage v chronic renal disease. 2003. K/DOQI guidelines (guidelines 1.3 and 6)*

Parameter	Goal
Ca (mg/dL)	8.5-9.5
P (mg/dL)	3.5-5.5
CaxP (mg^2/mL^2)	< 55
iPTH (pg/mL)	150-300

*Reference 1.

Ca and P determinations are done monthly and iPTH every 4 months. Ca and P levels have been determined by the standard colorimetric procedure and iPTH by chemiluminescence (DPC, Immulite 2000).

Administered therapies were: intestinal phosphorus chelating agents (calcium carbonate, calcium acetate, sevelamer, and less used aluminum hydroxide), and oral or intravenous 1,25 (OH)2 vitamin D3, monthly adjusted according to analytical data and protocols of each hemodialysis unit.

Data are analyzed with Nefrosoft HD 3.0 and SPSS softwares. The results are expressed as percentages and mean (SD, or median according to their normal distribution. Cut-off points are established according to K/DOQI 2003 guidelines (table I).

RESULTS

Total Ca and corrected Ca levels are within the normal range (mean (SD: 8.9 ± 0.6 mg/dL and 9.2 ± 0.7 mg/dL, respectively); however, 53.7% of them have normocalcemic values, whereas 9.1% had hypocalcaemia, and 37.1% had hypercalcaemia.

Phosphorus values are also within normal range (mean (SD: 5.0 ± 1.3 mg/dL); however, only 57.1% had values within the normal range, whereas 11.7% had hypophosphatemia, and 31.1% hyperphosphatemia.

The Ca (P value was within normal range (mean (SD: 46.3 ± 13.3 mg^2/mL^2). Although 71.7% of the patients had normal Ca (P value, 4.9% had levels above 800 pg/mL (figs. 1 and 2).

Median iPTH (its distribution is not normal) had an acceptable value of 253 pg/mL, but only 31.1% had a value within normal range whereas 25.1% had decreased values and 43.7% had hyperparathyroidism range, among which 9.3% had levels above 800 pg/mL (figs. 1 and 2).

The results are summarized in table II.

We found a linear correlation between P values and iPTH values (Figure 3). The percentage of cases with hyperphosphatemia was higher in the group of patients with iPTH values higher than 300 pg/mL (40% *vs* 23.3%, chi2 p = 0.006), as shown in figure 4.

We have found a relationship between Ca (P values and iPTH levels (table III). Among patients with iPTH within the normal range, 78.6% had normal Ca (P, whereas 3.6% had decreased Ca (P, and the remaining 17.8% had increased Ca (P. By contrast, only 35.2% of the patients with normal Ca (P value had iPTH levels within an acceptable range. Finally, when analyzing global results, only 25.2% of the pa-

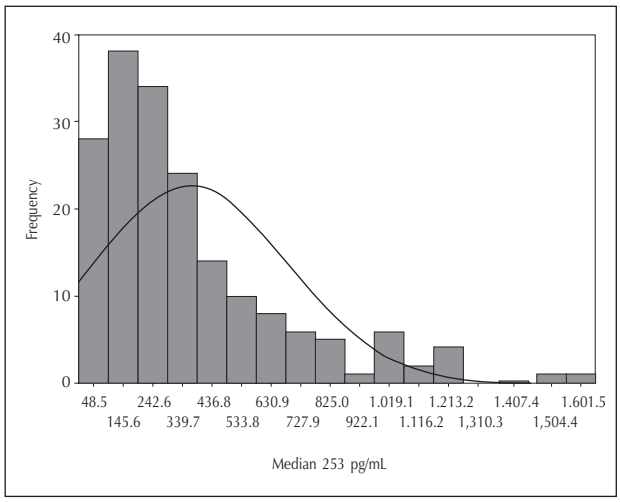

Fig. 1.—Histogram of serum iPTH values.

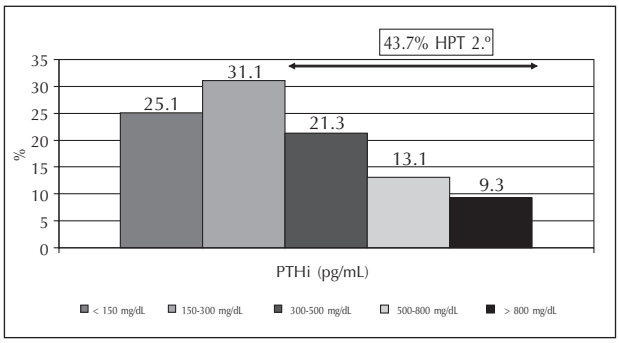

Fig. 2.—Distribution of percentages pf serum iPTH values.

Table II. Values of Ca-P metabolism

Parameter	Value	% patients with values under normal rage	% patients with values above normal rage	% patients with out of range values
Ca_{alb} (mg/dL)	9.2 ± 0.7*	9.1	37.1	46.2
P (mg/dL)	5.0 ± 1.3*	11.7	31.1	42.8
Ca_{alb}xP (mg^2/mL^2)	46.3 ± 13*	4.9	23.4	28.3
iPTH (pg/mL)	253**	25.1	43.7	68.8

*mean ± SD
**median.

tients had all 4 markers within the normal range, and 17% had all the parameters out of range.

DISCUSSION

In our work, we could verify that control of Ca-P metabolism in hemodialysis patients is clearly insufficient when taking as reference the values indicated in 2003 DOQI guidelines. These Guidelines have indicated the ranges for Ca, P, Ca (P, and iPTH values, out of which there is an increased risk for complications.4 The goals are based on expert opinion in the USA, but they have reached the level of almost universal evidence after the outcomes analysis performed at most of dialysis units in several European countries and in Japan. Besides, these guidelines are helpful to assess the results and plan therapies, although they have set normal intervals difficult to achieve.[5-7] It is striking that in most of published studies, many patients have cited parameters out of the established range, either decreased or increased, in both cases associated to complications. Thus, in Alyís et al.[2] study, only 7% of patients had all four

Table III. Distribution of values of Ca (P and iPTH)

iPTH (pg/mL)	< 150	150-300	300-500	500-800	> 800
Ca_{alb} x P (mg^2/mL^2)					
< 28	13.6	3.6			
28-55	70.5	78.6	82.9	59.1	47.1
> 55	15.9	17.8	17.1	40.9	52.9

Chi^2, p = 0.001.

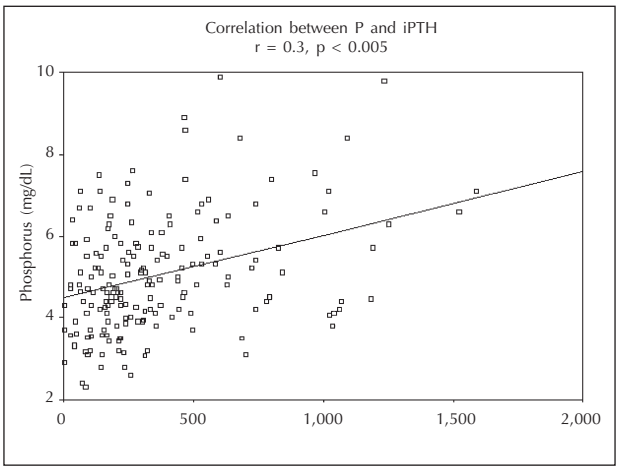

Fig. 3.—Correlation between serum P and iPTH.

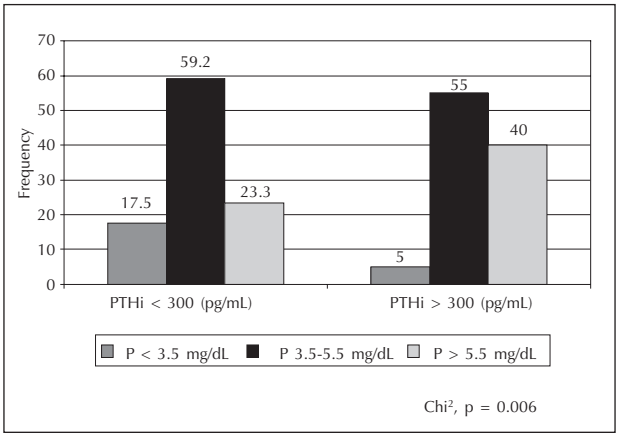

Fig. 4.—Relationship between serum iPTH and phosphorus.

parameters within the range. In Gallieniís results, the outcomes are not very dissimilar, and point out the difficulty to control P and iPTH levels.[8] The multicenter study known as «Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS I and II)»4, performed in 7 countries (France, Germany, Italy, England, Spain, USA, and Japan), gathering several issues of dialysis patients, allows for comparison of the outcomes of Ca-P metabolism control. Again, it is shown that complete control is only obtained in 4.6-5.5% of the patients, with certain, although not striking, differences between countries. In our Country, GÚrriz et al. detected that of 2392 dialyzed patients at the Autonomous Community of Valencia, only 7.3% of them had all 4 parameters within the normal range.[9] Besides, in a multicenter study performed on 7512 cases, Cannata et al.[10] showed that only 13% had Ca (P and iPTH levels under control. Our results may be improved, since only a forth of patients meet the four criteria, and 17% none of them. Besides, we confirm that the worst controlled parameter is iPTH, with 25.1% of patients within the range of adynamic bone disease and a little bit less than half with hyperparathyroidism, with a severe range in 9.3%. To make results even somber, 58.5% of patients with increased Ca (P had elevated iPTH levels, with the possible risk of vascular and soft tissue calcifications. On the other hand, adynamic bone disease associated to decreased values of iPTH is also complicated with musculoskeletal pathology (osteomalacia) and vascular calcifications, and increased mortality.[11,12] Besides, chronic hypophosphatemia, as a reflection of hyponutrition, is associated to many complications and, of course, to decreased survival. It has been recently reported that even patients with normal Ca (P may be on risk for vascular complications if there is a concomitant fetuin A deficit, an inhibitor of systemic calcification.[13] We would like to point out not only the difficulty in achieving the mentioned parameters but also to maintain them; thus, Walters et al.[14] reported that adequate control decreases to 3% within 6 months, from 11%.

We have found a relationship between P and iPTH levels, without being able to establish a causal relation, although it may be possible that hyperphosphatemia will be one of the stimulating factors of PTH synthesis. In our patients, P control has been very difficult, which taken together with other factors has contributed to the elevated prevalence of secondary hyperparathyroidism. In fact, the correlation between P and iPTH is weak although statistically significant, with r^2 of 0.09, which supports the existence of other factors (vitamin D decrease, skeletal PTH resistance, among other), which favors PTH synthesis and release.

Dialysis patients have an unacceptable increased cardiovascular morbidity and mortality. On the other hand, impairments of mineral and bone metabolism lead to vascular lesions and early and accelerated arteriosclerosis. Therefore, Ca-P metabolism control is necessary to reduce musculoskeletal complications and decrease morbimortality. In our country, Marco et al.[15] have described that mineral metabolism impairments are clearly with deaths of cardiovascular origin. In this sense, Block et al.[3] have also shown that Ca-P metabolism changes studied in 40,538 dialyzed patients in the USA are associated with increased cardiovascular morbimortality. Although these works do not have as reference the guidelines ranges, the results from the DOPPS study have con-

firmed these conclusions,[4,16] possibly by an increment and progression of vascular calcifications.[17] The Answer study has recently analyzed in our country the data from 2407 incident patients on hemodialysis. Again, the results of Ca-P metabolism are far from commented goals, and once again, the worst controlled parameter is iPTH, where only 29% are within the normal range.[18] Although the results from patients starting on hemodialysis cannot be compared to those obtained in our work, where we studied patients with at least 3 months on hemodialysis, it is foreseeable that long-term results will be far from desired values.

As it can be deduced from most of publications that compare their results with DOQI guidelines, outcome analysis of Ca-P control in dialysis should be done by means of percentage of patients out of range since both increased and decreased values for each one of the parameters are harmful. Therefore, values of central tendency measurement, such as means and medians, may be acceptable but do not reflect the number of insufficiently controlled cases. And it is precisely with these patients in whom it is worthy to reconsider the treatment since, with currently available measures, it is impossible to completely control each one of the parameters, as we have been able to observe in our work, and even some therapies may be beneficial for some parameters and harmful for others, as it occurs with Ca-containing intestinal P chelating agents.[5,7,17] It is likely that new therapies for Ca-P metabolism impairments (P-chelating agents free of calcium, vitamin D analogues, calcium-mimetics) may help controlling the parameters within the DOQI ranges[19-20], and thus, decrease associated morbimortality. It is our opinion that new commented therapies should not be prescribed to all dialysis patients for two reasons: their side effects, and their high cost. It seems more reasonable, therefore, to select patients (and for this DOQI guidelines are very helpful(that do not respond to usual measures in order to plan the new mentioned therapies. However, some time will have to go by until confirming that these guidelines are achievable and to what extend their accomplishment reduces long-term morbimortality.[7]

We conclude that Ca-P metabolism is insufficient and it is a non-solved problem in dialysis units. The analysis of adaptation to parameters of the Ca-P metabolism to 2003 k/DOQI guidelines should be done using percentages in order to know the group of patients that may benefit from new therapies to try to reduce mortality and bone and cardiovascular complications.

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