Spanish nephrologists and the management of mineral and bone metabolism disorders in chronic kidney disease

Jorge Cannata-Andía[1], J. Vicente Torregrosa[2]

[1] Servicio de Metabolismo Óseo y Mineral. Hospital Universitario Central de Asturias. Instituto Reina Sofía de Investigación. REDinREN del ISCIII. Universidad de Oviedo. Oviedo, Asturias (Spain)

[2] Servicio de Nefrología y Trasplante renal. Hospital Clínic. REDinREN del ISCIII. Barcelona (Spain)

Nefrologia 2014;34(2):175-88

doi:10.3265/Nefrologia.pre2014.Jan.12280

ABSTRACT

This study was designed to assess the current perception of Spanish nephrologists in the clinical management of mineral and bone metabolism disorders in chronic kidney disease (CKD-MBD). As such, we used a semi-structured distance professional consensus procedure via e-mail (modified Delphi method) on a representative nephrologist panel, under the direction of a coordinating committee. To analyse the group's opinion and the type of consensus reached on each issue raised, we used the median of the group's scores and the "level of agreement" reached by those surveyed. On a total of 86 issues, a consensus agreement and disagreement was achieved in 70 (81.4%), of which 60.5% (52 items) agreed with the statement and 20.9% (18 items) disagreed. In 16 items (18.6%), there was insufficient unanimity in the panel's opinion, either due to professional opinion disparity or due to the lack of opinion established in the majority of the expert committee. Accepting the study's limitations, we considered that the items for which there was a consensus reinforce some CKD-MBD concepts with their impact on daily clinical practice and allow the degree of homogeneity that we could expect in this area to be assessed. The items in which there was no consensus help us to know the areas of uncertainty and are very useful for clarifying which aspects have a greater need for further knowledge and which areas require prospective studies to be conducted to improve the management of these disorders.

Keywords: Delphi method. Parathyroid hormone. Calcium. Phosphorus. Vitamin D. Calcimimetics. CKD-MBD.

Correspondence: Jorge Cannata Andía
Servicio de Metabolismo Óseo y Mineral.
Hospital Universitario Central de Asturias, C/ Julián Clavería, s/n.
33006, Oviedo. (Spain).
cannata@hca.es
vtorre@clinic.ub.es

Los nefrólogos españoles y el manejo de las alteraciones del metabolismo óseo-mineral en la enfermedad renal crónica

RESUMEN

El presente estudio fue diseñado para evaluar la percepción actual de los nefrólogos españoles en el manejo clínico de las alteraciones del metabolismo óseo y mineral en la enfermedad renal crónica (CKD-MBD). Para ello se empleó un procedimiento semiestructurado de consenso profesional a distancia, por correo electrónico (método Delphi modificado), a un panel representativo del colectivo nefrológico, bajo la dirección de un comité coordinador. Para analizar la opinión grupal y el tipo de consenso alcanzado sobre cada cuestión planteada, se empleó la posición de la mediana de puntuaciones del grupo y el «nivel de concordancia» alcanzado por los encuestados. Sobre un total de 86 cuestiones se logró un consenso en acuerdo y desacuerdo en 70 (81,4 %), de los cuales un 60,5 % (52 ítems) lo fueron en términos de acuerdo con la aseveración y un 20,9 % (18 ítems) en desacuerdo. En 16 ítems (18,6 %) no se consiguió suficiente unanimidad de criterio en el panel, bien por disparidad de opinión profesional, bien por falta de criterio establecido en una mayoría del comité de expertos. Aceptando las limitaciones del estudio, consideramos que los ítems en los que hubo consenso refuerzan algunos conceptos de CKD-MBD con su repercusión en la práctica clínica diaria y permiten valorar el grado de homogeneidad que podríamos esperar en esta área. Los ítems en los que no hubo consenso nos ayudan a conocer las áreas de incertidumbre y resultan de gran utilidad para precisar en qué aspectos existe una mayor necesidad de profundización y de emprender estudios prospectivos que permitan mejorar el manejo de estas alteraciones.

Palabras clave: *Método Delphi. Hormona paratiroidea. Calcio. Fósforo. Vitamina D. Calcimiméticos. CKD-MBD.*

INTRODUCTION

Mineral and bone metabolism disorders in chronic kidney disease (CKD-MBD) is a very dynamic field of study, which

has experienced a lot of changes, especially over the last five years.

Other factors have been added to the group considered to be the "classic regulators of mineral and bone metabolism" (calcium, phosphorus, parathyroid hormone [PTH] and calcitriol), some already known, such as calcidiol, and others new, such as fibroblast growth factor 23 (FGF-23) and klotho.[1] Furthermore, other disorders that until recently were considered outside the area of CKD-MBD, such as vascular calcification, cardiovascular disease and bone fractures, have progressively become part of the CKD-MBD[2] group.

Along with these changes and advances in the knowledge of CKD-MBD, new drugs have been marketed for controlling its disorders, which, although potentially offer more flexibility and a better therapeutic range, have increased the number of question marks about their efficacy and limitations of use in daily practice.

Most of these issues have been addressed in the recent clinical practice guidelines, amongst them those of 2009 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD, which have been revised again at the end of 2013,[2] and the CKD-MBD Guidelines of the Spanish Society of Nephrology (S.E.N.).[3] However, there is still significant uncertainty that results in major variations in the clinical management of these disorders, and we will be exploring this area in our study.

This study was designed to assess Spanish nephrologists' current perception of the clinical management of CKD-MBD disorders.

MATERIAL AND METHOD

To assess Spanish nephrologists' perception of mineral and bone metabolism, we used a semi-structured remote professional consensus procedure via e-mail (modified Delphi method),[4,5] allowing for contemplative and equal participation by a representative nephrologist panel. It required successive rounds of a structured survey (with closed-ended question scales), with processing and return of intermediate results to participants in order that they could confidentially compare their personal opinions with those of the other panellists.

The project was developed over four phases (Figure 1): 1) Formation of a scientific committee comprising 10 nephrologists with a special interest in the area of mineral and bone metabolism, responsible for leading the project and the task of developing a questionnaire, proposing expert panellists, analysing and interpreting the results and drawing final conclusions. 2) Selection of an expert panel: the scientific committee chose 59 nephrologists representing all regions of Spain, interested in the area of mineral and bone metabolism, who met the requirements detailed above on the basis of a pre-selection of 192 nephrologists and who worked mainly in the areas of dialysis, pre-dialysis and renal transplantation. 3) The expert panel received the survey with the statements, which they responded to via e-mail in two rounds. 4) Analysis and discussion of these results in a joint face-to-face meeting between the scientific and expert committees.

A technical team was also required, which was responsible for implementing the method, editing and distributing the first questionnaire, analysing the responses of the first round, the provisional report and distributing the second questionnaire, analysing the second questionnaires and statistical interpretation of the consensus reached.

Developing the questionnaire and method of response

We initially defined the systematic literature review and questionnaire development procedure. Each item on the questionnaire was a statement (positive or negative) on an opinion regarding CKD-MBD disorders in any aspect of interest or controversy. After reviewing and grouping the items proposed by subject, we developed a final version of the questionnaire, which included 86 items and was accepted by the scientific committee and divided into the following subject sections:

- Phosphorus, calcium and magnesium metabolism.
- Bone and cardiovascular system.
- Vitamin D.
- Calcimimetics, parathyroidectomy and associations with vitamin D.
- Renal transplantation.

Assessment scale of the clinical recommendations being judged

In order to assess the issues, one 9-point Likert-type ordinal scale was proposed, which was similar to the conventional format (UCLA-Rand Corporation) used for comparative assessment and prioritisation of different health options (technologies, etc.).[6,7] The response categories were defined using linguistic qualifiers of agreement/disagreement grouped into three regions, with the proposals presented as the following possible conclusions:

- 1-3: I disagree with the statement (the lower the score, the higher the degree of disagreement).
- 4-6: I neither agree nor disagree with the statement; my opinion on the issue is not fully defined (4 or 6 is selected

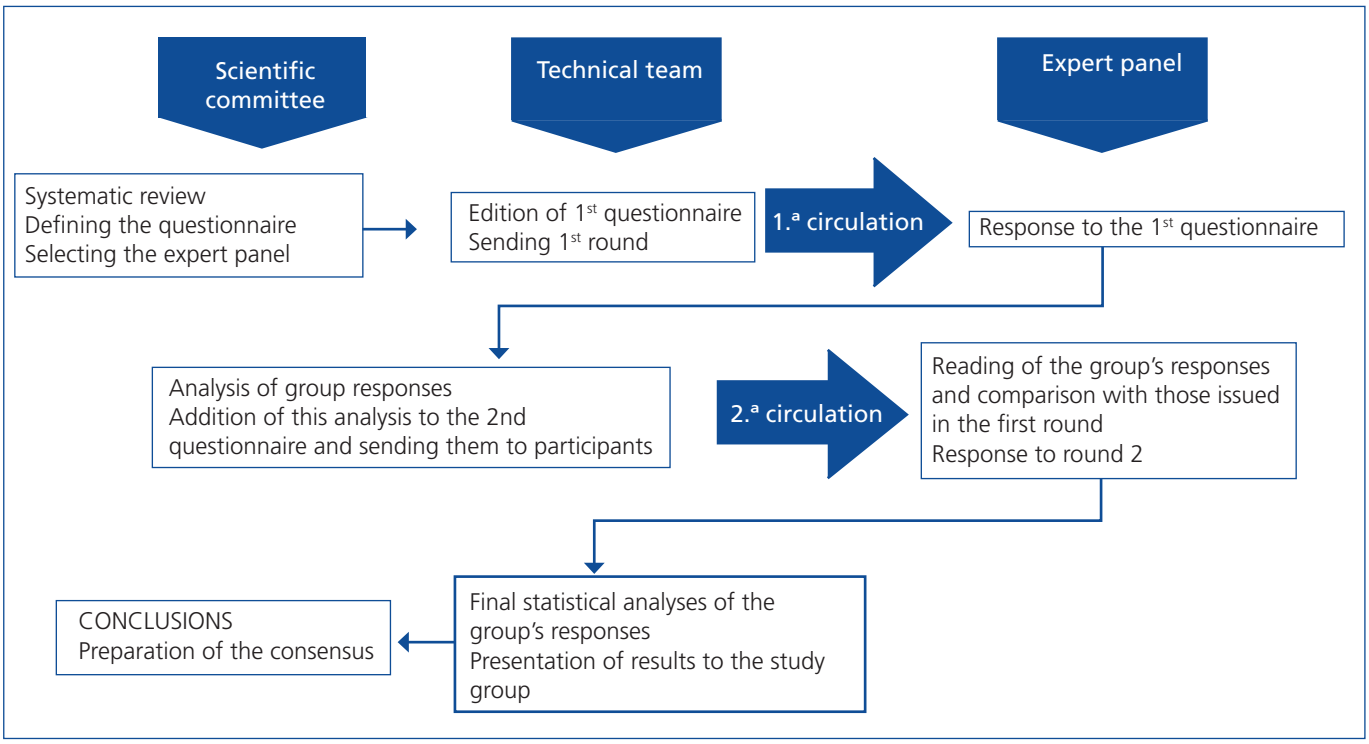

Figure 1. Delphi method flowchart. Study development diagram.

when the respondent is closer to disagreeing or agreeing, respectively).

– 7-9: I agree with the statement (the higher the score, the higher the degree of agreement).

The survey also offered the possibility of adding free comments to each item and a final section of new proposals for the committee to assess. For statistical purposes, unanswered statements were analysed as lost cases.

Analysis and interpretation of results

We performed a descriptive analysis of the responses using the median, mean and interquartile range with the specifications listed below. The comparisons were carried out using the mean with a 95% confidence interval. To assess the group's opinion and the type of consensus reached on each issue raised, we used the median group score and the "level of agreement" reached by those surveyed, in accordance with the following criteria: an item was considered to be agreed upon by consensus whenever there was "concordance" of opinion within the panel. In this case, the median value determined the group consensus reached, which was based on the three aforementioned groups: majority "disagreement" with the item if the median was ≤3; majority "agreement" with the item if the median was ≥7. Cases in which the median was between 4 and 6 were considered to be "uncertain" items for the majority of the group and were not agreed upon by consensus. We established that there was "discordance" in the panel whenever the percentage of panellist responses against (those whose score was outside the region containing the median for this item) was higher than 33%. The remaining items in which we did not observe concordance or discordance were considered to have an "undetermined" level of consensus.

All the items for which the group did not achieve a clear consensus for or against the issue raised (uncertain items, those in which discordance was observed and those that showed an undetermined level of consensus) were proposed for the panel's reconsideration in the second Delphi round (Figure 1). The items in which a significant spread of opinions was observed amongst those surveyed were also re-assessed, with an interquartile range ≥4 points (range of scores between the p25 and p75 values of the distribution).

Between both rounds, the panellists were informed of the detailed distribution of the group's anonymous responses in the first survey (through bar graphs) and comments and clarifications contributed by each participant were provided anonymously.

After reviewing this information, we requested a new personal assessment of the items not agreed upon by consensus in the first round. After the second round of the survey, identical

criteria were applied in order to distinguish the items definitively agreed upon by consensus from those in which it was not possible to homogenise the panel's opinion. The total time in which the two rounds were carried out was two months.

For the purpose of comparing graphs between items, we calculated the panellists' average scores for each statement with a 95% confidence interval. The more extreme the average score of an item (closer to 1 or 9), the more we considered that either an agreement or a disagreement consensus, respectively, was achieved on the proposal expressed by each item.

A smaller confidence interval was interpreted as an expression of greater unanimity of opinions in the group. The items in which no consensus was achieved after the process described was completed were analysed descriptively to distinguish whether this situation was due to discordance of opinion or due to a majority of the panel's opinion being uncertain with respect to the item (the majority of the group said they did not have a definitive opinion; response = 4-6).

RESULTS

Out of a total of 86 statements, an agreement and disagreement consensus was achieved in 70, that is, a sufficient consensus was achieved in 81.4%, of which 60.5% (52 items) agreed with the statement and 20.9% (18 items) disagreed. In 16 items (18.6%), sufficient unanimity was not achieved in the panellist's opinions, either due to a disparity of professional opinion, or due to the lack of opinion in a majority of the expert committee. In the first round, there was a consensus in 40 out of the 86 statements analysed (34 in agreement and 6 in disagreement). Of the 46 remaining items proposed for the experts' reconsideration in the second round, a consensus was reached in 30 more (18 in agreement and 12 in disagreement) (Table 1). The results/conclusions detailed below group together the key aspects of this consensus.

Table 1. Statistical results for the 86 statements

I. VITAMIN D				
	Median	**% panellists against**	**Average**	**Interquartile range**
General aspects: assessment and supplementation of vitamin D in CKD				
1. The level of 25(OH)D3 (calcidiol) should be 25-40ng/ml at all stages of CKD	7	21.60	7.02	1
2. Patients older than 65 years of age require similar doses of calcidiol at any stage of CKD as those younger than 65 years of age at any stage of CKD*	5	68.00	5.20	4
3.The correction of vitamin D deficiency/insufficiency should be carried out both in early stages of CKD (1-2) and in stages 3-5 or in dialysis	8	11.50	7.48	1
4. The adverse effects of vitamin D supplementation for correcting deficiency/insufficiency are the same in early stages of CKD as in stages 3-5 or in dialysis	3	12.20	3.22	0
5. The administration of native vitamin D along with active vitamin D analogues is fully justified for inhibiting the FGF-23 in the initial stages of CKD*	6	60.50	4.81	3
6. Measuring 1,25(OH)2 D3 (calcitriol) is useful from the clinical point of view	3	32.70	3.52	3
First scenario: stages 2-5 CKD (pre-dialysis)				
7. It is essential to test calcidiol and calcitriol in patients with stages 2-4 CKD	3	9.60	3.06	0
8. Both should be tested during each patient visit to the clinic, independently of previous values and the treatment established	3	17.60	2.90	1
9. Native vitamin D or calcidiol may be toxic in high doses, and as such, it is necessary to carry out systematic controls of plasma creatinine, calcium and phosphorus	8	17.30	7.67	2

Continues on next page>

Continues Table 1. Statistical results for the 86 statements

	Median	% panellists against	Average	Interquartile range
10. For calcitriol, the initial dose should be 0.25 micrograms on alternate nights	7	15.40	7.17	1
11. If a phosphate binder had to bind to active vitamin D metabolites, those that contain calcium should be avoided	7	26.00	6.96	2
Second scenario: stage 5D CKD (dialysis)				
12. In dialysis patients, treatment with native vitamin D or calcidiol added to treatment with active vitamin D (calcitriol or paricalcitol) favours hyperphosphataemia	7	26.90	6.94	2
13. In dialysis patients, only active vitamin D (calcitriol/paricalcitol) should be recommended	3	15.40	2.58	2
14. If native vitamin D or calcidiol are used, it is preferable to combine them with paricalcitol to reduce the risk of hypercalcaemia and hyperphosphataemia	7	13.70	6.63	0
15. The combination of native vitamin D or calcidiol with active vitamin D makes it necessary to decrease the doses of both	7	7.80	6.98	0
16. For peritoneal dialysis patients, the same strategy should be employed as for haemodialysis patients in relation to vitamin D use	7	19.20	6.54	0
17. In haemodialysis or peritoneal dialysis patients, whenever vitamin D is used, it should be combined with non-calcium phosphate binders	7	46.00	5.50	4
II. CALCIMIMETICS, PARATHYROIDECTOMY AND COMBINATIONS WITH VITAMIN D				
18. Treatment for secondary hyperparathyroidism should start when the PTH level (pg/ml) is higher than 300*	7	31.40	5.75	4
19. The start of treatment for secondary hyperparathyroidism is independent of phosphataemia levels	3	15.40	3.15	1
20. The initial treatment for decreasing PTH levels are calcimimetics	2	13.50	2.48	2
21. The combination of VDR activators with calcimimetics achieves the control of PTH levels in 50-75% of all cases	8	7.33	11.80	1
22. Paricalcitol use is independent of calcium and/or phosphorus levels	3	23.10	2.83	2
23. Calcitriol use is independent of calcium and/or phosphorus levels	2	9.60	2.08	2
24. Calcimimetic use is independent of calcium and/or phosphorus levels	2	21.60	2.90	2
25. Paricalcitol use is appropriate for controlling vascular calcifications, even when PTH levels are controlled*	6	64.00	5.64	2
26. Calcimimetic use is appropriate for controlling vascular calcifications, even when PTH levels are controlled*	5	35.40	5.29	1
27. Both paricalcitol and calcimimetics protect against vascular calcifications	7	28.60	6.57	1
28. The presence of vascular calcifications influences the choice of treatment for secondary hyperparathyroidism	8	12.00	7.50	1
29. Parathyroidectomys should be indicated if PTH levels are higher than 1000 in spite of intensive treatment	8	8.00	7.60	1

Continues on next page>

Continues Table 1. Statistical results for the 86 statements

	Median	% panellists against	Average	Interquartile range
30. Phosphorus levels should be taken into account when indicating a parathyroidectomy	7	32.70	6.81	2
31. A PTH level less than 100 in dialysis patients means that it is necessary to use a low-calcium dialysate*	7	35.30	6.10	1
32. In kidney transplant patients, treatment with calcimimetics should continue if PTH has been difficult to control	7	16.00	6.76	0
33. In kidney transplant patients, calcimimetic use is appropriate for controlling calcium	7	25.50	6.43	1
34. In kidney transplant patients, calcimimetic use is appropriate for controlling phosphorus*	3	38.50	3.85	2
III. METABOLISM OF PHOSPHORUS, CALCIUM AND MAGNESIUM				
35. In CKD, there is an overload of phosphorus in the body before hyperphosphataemia appears	8	5.80	7.73	2
36. Testing FGF-23 is a good method for assessing phosphorus overload in the body before hyperphosphataemia appears	7	15.70	6.92	0
37. Phosphaturia in 24-hour urine has a value equivalent to the fraction of phosphorus excreted for assessing phosphorus overload in the body before hyperphosphataemia appears	7	8.70	6.90	0
38. Serum calcium does not represent the net balance of calcium intake, as overload is possible with normal calcaemia	7	11.80	7.41	1
39. A reasonable restriction of the lactoprotein diet (two rations [±120g] of animal proteins and one or two of dairy products) does not lead to a risk of malnutrition and contributes to controlling mineral metabolism in dialysis patients	7	23.50	6.73	0
40. It is considered reasonable to maintain a diet that is not restrictive in proteins in combination with an effective phosphate binder	7	18.00	6.60	0
41. The availability and absorption of phosphorus from animal protein and preservative intake is significantly higher than phosphorus that accompanies vegetable proteins	7	21.20	6.98	1
42. Patients should only receive phosphate binders if phosphorus higher than normal laboratory values is detected (for example >4.5mg/dl)	7	23.50	6.37	0
43. Patients should only receive phosphate binders if phosphorus higher than values recommended in the data sheet is detected (for example >5.5mg/dl)	3	5.90	2.92	0
44. Aluminium hydroxide continues to be the most potent binder (useful for P >6.5mg/dl) and it does not seem to be harmful when it is used over short periods of time	7	23.50	6.98	1
45. Phosphate binders that contain calcium should be avoided in patients with vascular or valvular calcification even though serum phosphorus is within range	8	15.40	7.37	1
46. Phosphate binders with calcium should only be used if PTH is clearly elevated	2	4.00	2.36	1
47. When a phosphate binder with calcium is used in a patient with stages 2-5 CKD, 1500mg of elemental calcium per day should never be exceeded	8	12.00	7.38	1

Continues on next page>

Continues Table 1. Statistical results for the 86 statements

	Median	% panellists against	Average	Interquartile range
48. When a phosphate binder with calcium is used in stages 2-5 CKD patients, calcium carbonate/calcium acetate/calcium acetate with magnesium carbonate should be used	7	21.60	6.45	0
49. Sevelamer carbonate should not be used as the first choice in patients with stages 2-5 CKD	3	28.80	3.94	2
50. Lanthanum carbonate should not be used as the first choice in patients with stages 2-5 CKD	3	26.90	3.81	2
51. Lanthanum carbonate may be used as the first choice of treatment in patients with stages 2-5 CKD and at risk (for example, with vascular or valvular calcification)	7	25.50	6.63	2
52. Lanthanum carbonate may be used as the first choice in patients with stages 2-5 CKD and at risk (for example, with vascular or valvular calcification) and hyperphosphataemia	8	12.00	7.34	1
53. If lanthanum and sevelamer carbonate were more affordable, they should be used as the first choice	7	25.50	6.86	2
54. Clinical data suggest a higher phosphate binding potency in lanthanum carbonate than in sevelamer carbonate	7	31.40	6.84	2
55. Knowing the serum magnesium levels and concentration is a prerequisite for the use of binders with magnesium	7	26.00	7.08	2
56. Gastrointestinal tolerance and the degree of adherence to the prescription are very important factors when using a phosphate binder without calcium	8	4.00	8.04	1
57. The combination of magnesium carbonate and calcium acetate as a phosphate binder is at least as effective as calcium binders without magnesium	7	32.70	6.37	2
58. In diabetes patients, no differential criteria is necessary in choosing a phosphate binder	3	21.20	3.48	0
59. Lanthanum carbonate is more favourable in terms of the cost/efficacy ratio than sevelamer*	7	50.00	5.92	2
60. Lanthanum and sevelamer carbonate have an advantage over calcium binders in terms of survival in the subpopulation over 65 years of age	7	20.00	6.70	0
IV. BONE AND CARDIOVASCULAR SYSTEM				
61. Vascular calcification has different causes and consequences according to the region of the vascular tree affected	7	11.50	7.19	1
62. Arterial rigidity caused by vascular calcification of the tunica media of the aorta is the factor that contributes most to cardiovascular morbidity and mortality	7	26.90	6.67	2
63. The ankle-brachial index should be monitored regularly in the cardiovascular assessment of CKD patients	7	23.10	6.81	1
64. Traditional cardiovascular risk factors should be controlled from early stages of CKD	9	0.00	8.41	1
65. In the prevention of vascular calcification, inflammatory foci should be controlled and treated (infections from catheters, purity of water, etc.)	8	6.00	8.02	2
66. The mechanisms involved in vascular and bone mineralisation are independent	3	9.60	3.23	0

Continues on next page>

Continues Table 1. Statistical results for the 86 statements

	Median	% panellists against	Average	Interquartile range
67. More severe vascular calcification is not associated with lower survival	2	12.00	2.44	1
68. The severity and progression of vascular calcification is associated with greater demineralisation	7	7.70	6.83	0
69. Osteoporotic fractures and a low bone mass are associated with higher mortality	8	14.00	7.38	1
70. Bisphosphonates, the reference treatment in osteoporosis, may be used in practice to reduce vascular calcifications*	5	38.40	5.46	2
V. TRANSPLANTATION				
71. PTH and calcidiol should be tested every six months in kidney transplant patients	7	21.60	6.92	1
72. A simple dorsolumbar x-ray should be performed in all patients who receive a kidney transplant, in order to assess the presence or risk of vertebral fracture	7	15.40	7.13	1
73. Mineral and bone density should be tested using DEXA in all patients who receive a kidney transplant	7	23.10	6.67	0
74. Kidney transplant patients should be supplemented as well as the rest of the general population in order to maintain normal serum calcidiol values	7	22.00	7.28	1
75. Treatment with active vitamin D (calcitriol, alfacalcidol or paracalcitol) is effective for preserving the post-transplant loss of bone mass	7	11.80	6.86	0
76. In transplant patients, any bisphosphonate may be used; there is no preferred bisphosphonate or route of administration (intravenous, oral)*	5	28.80	4.69	1
77. Dialysis patients who receive calcimimetics should maintain treatment after renal transplantation*	5	53.80	4.65	3
78. Post-transplant hypercalcaemia secondary to persistent hyperparathyroidism should be treated with calcimimetics	7	25.50	7.08	2
79. Post-transplant hypophosphataemia with elevated PTH should be treated with calcimimetics and the administration of oral phosphorus should be avoided*	6	60.70	5.57	2
In patients with post-transplant hypercalcaemia who start treatment with calcimimetics, these agents should be discontinued:				
80. After 6 months*	5	25.60	4.60	0
81. After 12 months*	5	24.50	4.63	0
82. They should not be discontinued if calcaemia control is correct*	7	42.00	6.04	2
If after a period of treatment with calcimimetics they are discontinued and hypercalcaemia reappears, the most appropriate attitude is:				
83. Recommence treatment	7	24.40	6.96	2
84. Indicate a parathyroidectomy	3	30.80	3.65	2
85. The continual administration of low doses of calcium (500mg/day) and some form of vitamin D is advisable for preserving bone mass in patients with steroid doses higher than 5mg/24h	7	26.50	6.69	1
86. Patients with kidney transplants and deterioration of renal function who have hyperphosphataemia may be treated with any phosphate binder	7	25.00	6.48	1

CKD: chronic kidney disease, FGF-23: fibroblast growth factor 23, PTH: parathyroid hormone, VDR: vitamin D recipients.

Statements in which a consensus was reached

The 52 items agreed on by consensus can be grouped into the following 36 following points:

1. In chronic kidney disease, there is an overload in the body of phosphorus before hyperphosphataemia appears. This overload may be assessed using the fraction of phosphorus excreted.
2. A dietary restriction of phosphorus intake should be attempted whenever overload is suspected. A reasonable dietary restriction of lactoprotein (2 rations [±120g] of animal proteins and one or two of dairy products) does not lead to a risk of malnutrition and contributes to controlling mineral metabolism in dialysis patients.
3. The availability and absorption of phosphorus from animal protein and preservative intake is significantly higher than phosphorus that accompanies vegetable proteins.
4. Patients should only receive phosphate binders if phosphorus higher than normal laboratory values is detected.
5. Aluminium hydroxide continues to be the most potent binder (useful for *P* >6.5mg/dl) and it does not seem to be harmful when it is used over short periods of time (2-3 months).
6. Phosphate binders that contain calcium should be avoided in patients with chronic kidney disease and vascular or valvular calcification and when they are used, 1500mg of elemental calcium per day should not be exceeded.
7. The combination of magnesium carbonate and calcium acetate seems to be at least as effective as the rest of calcium binders, and, if used, serum magnesium should be monitored.
8. In patients with chronic kidney disease and either vascular or valvular calcification who have hyperphosphataemia, lanthanum or sevelamer carbonate may be used as the first choice.
9. Clinical and experimental data suggest a higher phosphate binding potency in lanthanum carbonate than in sevelamer carbonate.
10. Lanthanum and sevelamer carbonate have an advantage over calcium binders in terms of survival in the subpopulation over 65 years of age.
11. The high price of lanthanum and sevelamer carbonate may mean that they are not considered the first choice in all cases.
12. Gastrointestinal tolerance and the degree of adherence to the prescription are very important factors when using a phosphate binder.
13. Serum calcium does not represent the net balance of calcium intake, as overload is possible with normal calcaemia.
14. Vascular calcifications have different consequences according to the type and location and they are a factor that contributes to cardiovascular morbidity and mortality.
15. Bone and vascular mineralisation occur by similar mechanisms.
16. The severity and progression of vascular calcifications, bone fractures and a lower bone mass are related to and associated with higher morbidity and mortality.
17. Modifiable cardiovascular risk factors (traditional and non-traditional) should be prevented and treated at an early stage.
18. The correction of vitamin D deficiency should be carried out at all stages of chronic kidney disease or dialysis and calcidiol levels should be 25-40ng/ml at all stages of CKD.
19. 1,25(OH2) D3 measurement does not seem to be useful from a clinical point of view.
20. In chronic kidney disease, the administration of vitamin D may have adverse effects both in the doses recommended by the guidelines and in high doses, and as such, there should be strict monitoring of calcium, phosphorus and creatinine.
21. The adverse effects of vitamin D supplementation for correcting deficiency/insufficiency are the same in any stage of CKD.
22. For calcitriol prescription in patients with chronic kidney disease not on dialysis, the initial dose should be 0.25 micrograms on alternate nights.
23. In all stages of chronic kidney disease, if a phosphate binder had to be added to the administration of vitamin D metabolites, those that contain calcium should be avoided.
24. In dialysis patients, treatment with native vitamin D or calcidiol added to treatment with active vitamin D favours hyperphosphataemia and hypercalcaemia, and this is why it is necessary to reduce the dose of both; in these cases, it seems preferable to use paricalcitol in order to reduce this risk.
25. In relation to vitamin D use, in peritoneal dialysis the same strategy should be employed as in haemodialysis.
26. It is important to control phosphorus levels before beginning therapies designed to act directly on the production and secretion of PTH, such as calcimimetics and/or vitamin D receptor (VDR) activators.
27. There is an agreement on the efficacy of combining calcimimetics with VDR activators in order to reduce PTH levels. However, the choice of calcimimetics and/or VDR activators is determined by serum phosphorus and calcium values.
28. Parathyroidectomies should be performed if PTH levels are higher than 1000pg/ml in spite of medical treatment.
29. A simple lateral dorsolumbar x-ray should be performed in all patients who receive a kidney transplant, in order to assess the presence of vertebral fracture and test mineral and bone density.
30. PTH and calcidiol should be tested every six months in kidney transplant patients.
31. Kidney transplant patients should be supplemented with vitamin D, as well as the rest of the general population, in order to maintain normal serum calcidiol values.

32. Treatment with active vitamin D or vitamin D analogues has been demonstrated to be effective in reducing bone mass loss immediately after transplantation.
33. The continuous administration of low doses of calcium (500mg/day) and some form of vitamin D is advisable for preserving bone mass in patients with steroid doses higher than 5mg/24h.
34. It is advisable for post-transplant hypercalcaemia secondary to persistent hyperparathyroidism to be treated with calcimimetics. If after a period of treatment with calcimimetics they are discontinued and hypercalcaemia reappears, the most appropriate attitude would be to recommence calcimimetic treatment.
35. Calcimimetic administration should probably be maintained in transplant patients in whom their use was necessary for controlling severe secondary hyperparathyroidism before transplantation.
36. There is no phosphate binder of choice for treating patients with a kidney transplant and deterioration of renal function who have hyperphosphataemia.

Statements in which no consensus was reached

The 18 items not agreed on by consensus can be summarised in the following 9 points:

1. Diabetes patients probably require differential criteria in choosing the phosphate binder, but it is not clear what this criteria should be.
2. There are serious doubts as to whether patients older than 65 at any stage of chronic kidney disease require similar doses of calcidiol as those under 65 years of age.
3. It is not clear whether the administration of native vitamin D along with active vitamin D analogues is fully justified for inhibiting the FGF-23 in the initial stages of CKD.
4. It is not clear whether in dialysis patients, whenever vitamin D is used, it should be combined with non-calcium phosphate binders.
5. The group's responses were not homogeneous for the statement that secondary hyperparathyroidism should start to be treated whenever the level of PTH (pg/ml) is greater than 300.
6. There was no agreement with regard to whether paricalcitol or calcimimetic use is appropriate for controlling vascular calcifications whenever PTH levels are controlled.
7. There was also uncertainty with regard to whether a PTH level of less than 100 in dialysis patients means that it is necessary to use a low-calcium dialysate.
8. With regard to kidney transplant patients, there was no homogeneity on whether it is appropriate to use calcimimetics to control post-transplant hypophosphataemia, avoiding the administration of oral phosphorus, or whether dialysis patients who receive calcimimetics should maintain treatment after renal transplantation.
9. No stance was observed on when to discontinue calcimimetics in transplant patients who receive it for controlling hypercalcaemia.

DISCUSSION

To our knowledge, this is the first study designed to assess the perception of nephrologists, in this case Spanish nephrologists, in the clinical management of CKD-MBD. The study was carried out via the Internet and subsequently in a face-to-face meeting, using the modified Delphi method, which is a reliable remote consensus procedure already used in biomedical research,[4,5] which avoids the difficulties and disadvantages of face-to-face discussion methods. These include travelling, bias of influence and loss of confidentiality. The main advantages offered by the Delphi method are controlled interaction between panellists, the opportunity to reflect and reconsider personal opinions without losing anonymity and statistical validation of the consensus reached.

The Delphi method was developed in the 1950s by scientists of the Rand Corporation as a method for making informed decisions based on expert opinions.[8] Since then, it has been used to assess behaviour and decision-making in various sectors,[9-12] and also recently in areas of nephrology.[13-19] Despite having undergone some changes, it continues to be a viable approach for compiling expert opinions through a structured iterative process in which a consensus is developed.[20,21]

This process involves several interactions with participants who, in general, create two or more rounds of responses within a reasonable period of time, in our case two months. The results of first round of answers can be modified in the second round and it is even possible to propose other items based on comments from all participants.[22] Furthermore, the Delphi technique offers a series of specific advantages and this is particularly useful because it avoids obstacles commonly observed in other discussion groups, such as interpersonal influence and time constraints.[22-24]

With this technique, those surveyed do not know the identity of the other panellists and therefore, they are freer, with fewer personal and social limitations.[21] Furthermore, they can complete the questionnaire at their own leisure and not simultaneously with the other participants.[25] The Delphi method has the advantage that various techniques can be employed for its statistical analysis.[26]

In our study, we achieved a high degree of consensus in the first round and observations were made that were very useful for improving or modifying some statements in the second round. At the end of the study, a consensus was achieved in most items considered; in fact, it was higher than 80%, which shows high homogeneity in the management of CKD-MBD disorders by nephrologists.

It is important to underscore that, although some members of the scientific committee in this study and authors of this article participated in the development of the S.E.N.[3] and KDIGO[2] clinical practice guidelines, what they report in

this study does not represent their personal opinion or their interpretation of the 86 statements issued in the survey. Their role was to objectively summarise (without influencing the final result) the consensus reached by the 59 nephrologists surveyed, following the Delphi methodology in relation to what these nephrologists, who are particularly interested in the subject, believe about managing mineral and bone metabolism. These opinions may or may not be consistent with that recommended by the clinical practice guidelines,[2,3] but they are useful for communicating their degree of agreement, compliance, application and implementation in clinical practice. Therefore, the points of agreement and disagreement are a representation of the real situation and are the basis for the comments and thoughts described below in the discussion of these results.

There was agreement on the low usefulness of serum phosphorus and calcium levels for assessing their metabolism and that as renal function deteriorated there would be an overload of phosphorus and calcium. Nevertheless, at least with phosphorus, the panel considered that phosphate binders should not be used unless serum values of the latter are above the normal range. This widespread opinion of accepting that, despite a potential phosphorus overload there is still not sufficient evidence to start treatment with phosphate binders (statements 1 to 3), indicates a prudent attitude from nephrologists towards a subject that undoubtedly requires more scientific evidence before we aim for new indications of phosphate binders.

Furthermore, this attitude is consistent with recent results that have sparked controversy and suggest that, although in stages 3 and 4 chronic kidney disease there is a tendency towards phosphorus overload, thanks to the known compensatory phosphaturic mechanisms, mainly through FGF-23 and PTH, there would still not be significant phosphorus overload, but there would be an obvious calcium overload due to the kidney's inability to regulate the removal of the latter as renal function decreases.[27,28] Therefore, in stages 3 and 4 chronic kidney disease, the use of phosphate binders would not be indicated without hyperphosphataemia, and less still if calcium-containing binders were used, given that by avoiding a theoretical overload of phosphorus, we could aggravate rather than improve the situation, exposing patients to an unnecessary overload of calcium.[28,29] In line with this last concept, we observed the importance, given in the nephrologists' responses, to calcium overload, an aspect in which there was directly and indirectly agreement and homogeneity (statements 6 to 8 and 13 to 16) in considering it as a determinant of morbidity and mortality.

In the two sections related to other very important aspects in the management of CKD-MBD, such as the use of nutritional vitamin D, active forms of vitamin D, calcimimetics and when it would be necessary to replace medical treatment with parathyroidectomy, in general, there were more points of agreement than of disagreement, but there are still many gaps to be filled. Amongst them, due to their involvement in the routine management of patients, it is necessary to highlight the lack of consensus on PTH values that should be used for starting pharmacological treatment and on whether there is justification for combining the use of native vitamin D with active forms of vitamin D. This lack of agreement is not surprising, given that it reflects the uncertainty (due to lack of scientific evidence) in the recommendations of some clinical practice guidelines, such as the 2009 K/DIGO CKD-MBD guidelines.[2]

By contrast, there was a high degree of agreement in relation to the levels of PTH at which we should consider that there is therapeutic failure and perform a parathyroidectomy. The figure considered as the threshold was 1000pg/ml. This is consistent with that recently published by the COSMOS study, in which it was observed that Mediterranean countries consider this level to be the most appropriate, while Scandinavian countries would perform surgery with lower PTH levels of around 700pg/ml.[30] If we take into account the 2009 K/DIGO CKD-MBD recommendations and the recent preliminary results of the COSMOS study (consistent with previous studies), presented by the European Renal Association-European Dialysis and Transplant Association[31] on what PTH values should be considered acceptable, serum PTH of 700pg/ml would be a low value for indicating parathyroidectomy.

Lastly, there were also points of agreement and disagreement in relation to CKD-MBD, renal transplantation and calcimimetics. There was a consensus on the need for post-transplant calcimimetics to be related to the severity of pre-transplant hyperparathyroidism, but not on the need for it in the management of post renal transplantation hypophosphataemia.

To summarise, we believe that the information obtained through the Delphi consensus is practically useful, given that it describes the current situation of CKD-MBD in Spain and we have an insight into the thoughts and likely actions of Spanish nephrologists who are most closely related to the area of mineral and bone metabolism in the regular management of patients. As can be observed in the responses, this is not always consistent with that recommended by the guidelines,[2,3] but it does not necessarily represent inadequate clinical practice. In some cases, it probably does, but in others, it may be a basis for reconsidering some of the recommendations and, therefore, there is a need to regularly revise the guidelines with the objective of improving them and updating them in accordance with the new evidence available.

However, it is necessary to recognise that the consensus reached is in the context of a very specific setting and, as such, it has various limitations. Amongst them, we must highlight that it was restricted only to our country and to the group

surveyed (empirically classified a priori as experts), due to their special interest in the subject, but who do not represent the overall opinion of nephrologists or of many others who did not participate because of their lesser relationship with this subject, but who also participate in the management of CKD-MBD disorders.

Accepting the study's limitations, we considered that the items in which there was a consensus reinforce some CKD-MBD concepts with their impact on daily clinical practice and allow the degree of homogeneity that we could expect in this area to be assessed. As already mentioned, the items in which there was not a consensus help us to know the areas of uncertainty and are very useful for specifying in which aspects there is a greater need for further understanding and for carrying out prospective studies that allow the management of CKD-MBD disorders to be improved.

Acknowledgements

This study was possible thanks to the logistical support of Shire Pharmaceutical Ibérica and the backing of the Spanish Society of Nephrology. The technical team responsible for implementing the method and statistical analysis was Luzan 5.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

REFERENCES

1. Mejía N, Roman-García P, Miar AB, Tavira B, Cannata-Andía JB. Chronic kidney disease-mineral and bone disorder: a complex scenario. Nefrologia 2011;31(5):514-9.
2. Moe SM, Drüeke TB, Block GA, Cannata-Andía JB, Elder GJ, Fukagawa M, et al. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009;(113):S1-130.
3. Torregrosa JV, Bover J, Cannata Andía J, Lorenzo V, de Francisco AL, Martínez, et al. Spanish Society of Nephrology recommendations for controlling mineral and bone disorder in chronic kidney disease patients (S.E.N.-M.B.D.).Nefrologia 2011;31 Suppl 1:3-32.
4. Dalkey NC. The Delphi Method: an experimental study of group opinion. Santa Monica (California): Rand Corporation; 1969. Publication nº RM-59999 PR.
5. Dalkey N, Brown B, Cochran S. The Delphi Method, III: use of self ratings to improve group estimates. Santa Monica (California): Rand Corporation; 1969. Publication nº RM-6115-PR.
6. Likert R. A technique for the measurement of attitudes. Archives of Psychology 1932;140:1-55.
7. Carifio J, Perla R. Resolving the 50-year debate around using and misusing Likert scales. Med Educ 2008;42:1150-2.
8. Cornish E. The study of the future: an introduction to the art and science of understanding and shaping tomorrow's world. Maryland: World Future Society; 1977.
9. Kelly CM, Jorm AF, Kitchener BA. Development of mental health first aid guidelines on how a member of the public can support a person affected by a traumatic event: a Delphi study. BMC Psychiatry 2010;10:49.
10. Tran D, Hall LM, Davis A, Landry MD, Burnett D, Berg K, et al. Identification of recruitment and retention strategies for rehabilitation professionals in Ontario, Canada: results from expert panels. BMC Health Serv Res 2008;8:249-52.
11. Vandelanotte C, Dwyer T, Van Itallie A, Hanley C, Mummery WK. The development of an internet-based outpatient cardiac rehabilitation intervention: a Delphi study. BMC Cardiovasc Disord 2010;10:27-31.
12. van Stralen MM, Lechner L, Mudde AN, de Vries H, Bolman C. Determinants of awareness, initiation and maintenance of physical activity among the over-fifties: a Delphi study. Health Educ Res 2010;25(2):233-47.
13. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, et al. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: guideline methodology. Clin Toxicol (Phila) 2012;50(5):403-13.
14. Lindberg M, Lundström-Landegren K, Johansson P, Lidén S, Holm U. Competencies for practice in renal care: a national Delphi study. J Ren Care 2012;38(2):69-75.
15. Cantú Quintanilla G, Reyes A, Romero Navarro B, Luque Coqui M, Rodríguez Ortega G, Reyes R, et al. Usefulness of the Delphy method for reaching consensus in the allocation of deceased donor kidneys in six Mexican hospital. Cuad Bioet 2010;21(73):359-74.
16. Himmelfarb J, Joannidis M, Molitoris B, Schietz M, Okusa MD, Warnock D, et al. Evaluation and initial management of acute kidney injury. Clin J Am Soc Nephrol 2008;3(4):962-7.
17. Gibney N, Hoste E, Burdmann EA, Bunchman T, Kher V, Viswanathan R, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. Clin J Am Soc Nephrol 2008;3(3):876-80.
18. Murray PT, Devarajan P, Levey AS, Eckardt KU, Bonventre JV, Lombardi R, et al. A framework and key research questions in AKI diagnosis and staging in different environments. Clin J Am Soc Nephrol 2008;3(3):864-8.
19. Davenport A, Bouman C, Kirpalani A, Skippen P, Tolwani A, Mehta RL, et al. Delivery of renal replacement therapy in acute kidney injury: what are the key issues? Clin J Am Soc Nephrol 2008;3(3):869-75.
20. Gupta UG, Clarke RE. Theory and applications of the Delphi technique: A bibliography (1975-1994). Technological Forecasting and Social Change 1996;53(2):185-211.
21. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. Med Teach 2005;27(7):639-43.
22. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. Practical Asessment Research & Evaluation. 2007. Available at: http://pareonline.net/getvn.asp?v=12&n=10
23. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32(4):1008-15.

24. Dalkey NC, Rourke DL. Experimental assessment of Delphi procedures with group value judgments. In: Dalkey NC, Rourke DL, Lewis R, Snyder D, editors. Studies in the quality of life: Delphi and decision-making. Lexington, MA: Lexington Books; 1972. pp. 55-83.
25. Bowles KH, Holmes JH, Naylor MD, Liberatore M, Nydick R. Biomedical and Health Informatics: From Foundations to Applications: 2003; Washington, DC. AMIA 2003 Symposium Proceedings; 2003. Expert Consensus for Discharge Referral Decisions Using Online Delphi. pp. 106-9.
26. Linstone HA, Turoff M. In: Linstone HA, Turoff M, editors. The Delphi method, techniques and applications. 2002. Available at: http://www.is.njit.edu/pubs/delphibook/
27. Langman CB, Cannata-Andía JB. Calcium in chronic kidney disease: Myths and realities. Clin J Am Soc Nephrol 2010;5:S1-2.
28. Hill KM, Martin BR, Wastney ME, McCabe GP, Moe SM, Weaver CM, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. Kidney Int 2013;83:959-66.
29. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol 2012;23(8):1407-15.
30. Fernandez-Martin JL, Carrero JJ, Benedik M, Bos WJ, Covic A, Ferreira A, et al. COSMOS: the dialysis scenario of CKD-MBD in Europe. Nephrol Dial Transplant 2013;28:1922-35.
31. Fernández-Martín JL, Locatelli F, London G, Gorriz JL, Floege J, Ferreira A, et al.; on behalf of COSMOS. Cosmos: abnormalities in the main bone and mineral biochemical parameters are associated with higher risk of mortality. Nephrol Dial Transplant 2013;28 Suppl 1 (abstract).

ADDENDUM

Scientific committee

Jorge Cannata (Coordinator) (Hospital Central de Oviedo); **Jordi Bover** (Fundación Puigvert. Barcelona);); **Secundino Cigarrán** (Hospital da Costa Burela. Lugo); **Elvira Fernández** (Hospital Arnau de Vilanova. Lérida); **Emilio González Parra** (Hospital Fundación Jiménez Díaz. Madrid); **Víctor Lorenzo** (Hospital Universitario de Canarias. La Laguna. Tenerife); **Isabel Martínez** (Hospital de Galdakao. Bilbao); **Juan Navarro** (Hospital La Candelaria. Tenerife); **Mariano Rodríguez** (Hospital Universitario Reina Sofía. Córdoba); **José Vicente Torregrosa** (Hospital Clínic. Barcelona).

Expert panel

Francisco José Ahijado Hormigos (Hospital Virgen de la Salud. Toledo); **Jaume Almirall** (Parc Taulí de Sabadell. Barcelona. **Rafael Alonso Valente** (Complejo Hospitalario Universitario de Santiago de Compostela); **M.ª Luisa Amoedo Rivera** (Hospital General de Elche. Alicante); **Francisco José Ariza Fuentes** (Centro de Diálisis Fresenius Cabra. Córdoba); **Eduardo Baamonde Laborda** (Centro de Diálisis Avericum. Cádiz); **Guillermina Barril** (Hospital de La Princesa. Madrid); **Sergio Bea** (Hospital La Fe. Valencia); **Josep Calpe** (Diaverum Rotellar. Barcelona); (**Antonio Crespo Navarro** (Fresenius Gandía. Valencia); **Alfonso Cubas** (Hospital de Getafe. Madrid); **Antonio de Paula** (Hospital Universitario Río Hortega. Valladolid); (**Patricia de Sequera Ortiz**); (Hospital Infanta Leonor. Madrid); **Rodrigo Delgado Zamora** (Hospital Vírgen del Rocío. Sevilla); **Gloria del Peso** (Hospital de la Paz de Madrid); **Rafael Díaz-Tejeiro Izquierdo** (Hospital Virgen de la Salud. Toledo); **Amparo Fernández** (Fresenius Rambla Marina. Barcelona); **Adreu Foraster** (Diaverum Baix Llobregat. Barcelona); **Antonio Galán** (Hospital General Universitario. Valencia); **César García Cantón** (Hospital Insular de Las Palmas); **Gorka García Erauzquin** (Hospital de Cruces. Bilbao); **Sagrario García Rebollo** (Hospital universitario de Canarias); **Remedios Garofanos López** (Hospital de Torrecárdenas. Almería); **José Manuel Gil Junquero**); (Hospital General Ciudad de Jaén); **Miguel Ángel González** (Hospital Clínico. Valencia); **Enrique Gruss** (Hospital de Alcorcón. Madrid

); **José Antonio Herrero Calvo** (Hospital Clínico de San Carlos. Madrid); **M.ª Victoria Hidalgo Barquero** (Hospital de Zafra. Badajoz); **Emma Huarte** (Hospital San Pedro. Logroño); **María Jesús Izquierdo** (Complejo Asistencial Universitario de Burgos); **José Lacueva** (Alcer Liria. Valencia); **Luz Lozano** (Hospital de Fuenlabrada. Madrid); **Joaquín Manrique** (Complejo Hospitalario de Navarra. Pamplona); **Rosario Moreno López** (Hospital Militar. Zaragoza); **M.ª Antonia Munar** (Hospital Son Espasses. Mallorca); **Agustín Ortega** (Asyter. Albacete); **Magdalena Palomares Bayo** (Hospital Carlos Haya. Málaga); **María Parallé Alcalde** (CMD Montequinto. Sevilla); **Jesús Pérez** (Hospital Miguel Servet. Zaragoza); **Miguel Pérez Fontán** (Complejo Hospitalario Universitario de A Coruña); **Celestino Piñera** (Hospital Universitario Marqués de Valdecilla. Santander); **José Luis Pizarro** (Centro de Diálisis Diaverum. Málaga); **Dolores Prados Garrido** (Hospital San Cecilio. Granada); **Mario Prieto** (Hospital de León); **Constantino Fernández Rivera** (Complejo Hospitalario Universitario de A Coruña); **Minerva Rodríguez García** (Hospital Universitario Central de Asturias. Oviedo); **Esther Romero Ramírez** (Hospital Virgen de las Nieves. Granada); **Emilio Sánchez** (Hospital Universitario Central de Asturias. Oviedo **Dolores Sánchez de la Nieta García** (Hospital General de Ciudad Real); **Olga Sánchez García** (Hospital San Pedro de Alcántara. Málaga); **Ramón Saracho** (Hospital Santiago Apóstol. Vitoria); **Rafael Selgas** (Hospital La Paz. Madrid); **Jordi Soler** (Fresenius Reus. Tarragona); **Daniel Torán Montserrat** (Hospital General de Jerez. Cádiz); **Fernando Tornero Molina** (Hospital de Arganda. Madrid); **Martí Vallés** (Hospital Josep Trueta. Gerona); **Nicanor Vega Díaz** (Hospital Doctor Negrín. Gran Canaria); **Borja Zalduendo** (Hospital Donostia. San Sebastián).

Sent to review: 19 Sep. 2013 | Accepted: 21 Jan. 2014