REVIEW ARTICLE

Is the dietary protein restriction achievable in chronic kidney disease? The impact upon quality of life and the dialysis delay

Koulouridis E, Koulouridis I

Nephrology Department, General Hospital of Corfu, Greece

Abstract

The possible deleterious effect of meet consumption upon deterioration of renal disease was speculated from Lionel Beale as early as 1869. The first attempt to apply a very low protein diet in humans is attributed to Millard Smith who prescribed a diet consisting of 300 mg protein per day in a volunteer medical student for 24 days. Unfortunately, in early 20th century, prescribing very low protein diets among patients suffering from renal disease complicated with malnutrition and the medical practice of this era turned to the recommendation of high protein diets because it was believed that protein consumption is coupled with the strength of civilized man. In mid sixties Giordano and Giovanetti introduced low protein diets in the treatment of uremic patients but their efforts did not accepted from the medical community. Meanwhile the evolution of haemodialysis, peritoneal dialysis and transplantation as effective methods of treating end stage renal disease guided doctors and patients far from privative diets in the era of plenty. The rapidly increasing number of end stage renal disease patients needed substitution of renal function produced a tremendous increase of financial burden upon public health system expenditure and alternative measures of therapy, prevention and delaying chronic kidney disease searched. Unfortunately MDRD study failed to show convincing results of food protein restriction and blood pressure lowering in ameliorating deterioration of renal function and the majority of physicians turned to the practice of early dialysis in an attempt to avoid malnutrition. Despite the increasing knowledge and the appliance of certain guidelines in treating end stage renal disease patients, the morbidity and mortality remain high among this population. The search toward other possible toxic substances showed that phosphorus consumption with diet is another dangerous element exerting its deleterious effect in deteriorating renal function as well as increasing morbidity and mortality. Recently published epidemiological data suggest a very poor outcome of elderly patients, older than 80 years of age, undergoing substitution of renal function by dialysis or peritoneal dialysis and a lot of skepticism arise concerning the beneficial effect of diet and a rigorous effort of rehabilitation of these patients instead of substitution of renal function by either method. Hippokratia 2011; 15 (Suppl 1): 3-7

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Corresponding author: Koulouridis E,Nephrology Department. General Hospital of Corfu, 41 Spirou R str, 49100 Corfu, Greece, Tel. 0030-26610-33923, Fax: 0030-26610-22660, e-mail: koulef@otenet.gr

The role of low protein diets (LPDs) and phosphorus in chronic kidney disease (CKD).

Dietary protein restriction as a therapeutic measure in kidney disease has been introduced by Lionel S. Beale as early as 1869. Beale suggested protein restriction based upon the knowledge that the human organism metabolizes proteins to urea which is cleared from the kidney, therefore protein restriction ameliorates "kidneys work" and may protect them from further damage[1].

Very low protein diets were examined experimentally in humans by Millard Smith as early as 1926. He applied a very low protein diet, consisting mainly of carbohydrates and fat, in a volunteer medical student for 24 days. The diet provided a daily nitrogen intake of about 300 mg and 4000 caloriesThe only symptom experienced by the volunteer was nausea which subsided by the use of low nitrogen bread prepared from corn starch, India gum, yeast, sugar and salt. One year later Smith applied a very low protein diet (0,26 g/kg/day) in an azotemic patient for six months[2].

It has to be passed more than half a century (1931), after Beale's suggestion, when Newburgh LH showed that high nitrogen diets produce renal injury in rats. It is worthy to emphasize that these experiments showed no deleterious effect of pure protein (casein) upon kidneys and it was necessary to feed rats with animal tissues (dried liver or bovine muscle) in order to produce kidney damage[3]. After that, Lois L. MacKay and Thomas Addis showed that high protein diet as well as unilateral nephrectomy produces renal hypertrophy in rats. The renal size of two kidneys rats as well as the uninephrectomized rats was proportional to the amount of protein fed[4].

Although there was a considerable amount of evidence suggesting beneficial effect of low protein diet upon evolution of renal disease, the therapeutic efforts of physicians toward this direction ceased until the second half of 20th century, mostly because the two seniors on renal physiology of this period, namely Homer Smith and John P. Peters, did not accept the causative relation

between protein consumption and renal disease. On the other hand the advent of Second Word War turned the interest of physicians far from diets and after war termination new fields of investigation upon the cellular level emerged[1].

It was in the mid sixties when Giordano and Giovanetti showed that nitrogen free diets enriched with essential amino acids were capable to maintain nitrogen balance among uremic patients and more important to minimize or revert uremic symptoms[1,2], but unfortunately there is scant literature evaluating the clinical appliance of Giordano-Giovanetti diet among patients with chronic kidney disease during this period. The underlying mechanism of low protein diet's beneficial effect upon renal damage remained obscure until mid seventies when Shimamura and Morrison described the glomerulosclerosis occurring in 5/6 nephrectomized rats and attributed to hyperfiltration of the remnant nephrons[5]. The final solution of the relationship between protein consumption and kidney damage came from Barry M. Brenner and colleagues in 1979 with their experiments upon 5/6 nephrectomized rats. These investigators showed that the remnant nephrons increased single nephron glomerular filtration rate (snGFR) and developed glomerular and mesangial lesions which could be prevented by reducing the amount of protein feeding[6].

Accumulation of data at the beginning of eighties was enough to support an extensive implication of diet in treating renal diseases but, haemodialysis, peritoneal dialysis and renal transplantation facilities developed quickly during this period and physicians and patients unwillingness to be conformed under the requirements of food deprivation in the era of plenty swamped again the role of diet in treating the so called degenerative diseases. After that an enormous increase of the expenditures supporting these modalities of therapy exceeded any expectation of health providers and more importantly morbidity, mortality and life quality of these patients remains questionable until nowadays.

Under these circumstances, in 1989, the National Authorities of USA together with an expert advisory group of academic nephrologists sponsored and conducted a multicenter prospective study known as Modification of Diet in Renal Disease (MDRD) study in order to test the hypothesis that dietary protein restriction and blood pressure lowering are capable to slow the progression of renal disease among 1.840 patients with various stages of chronic kidney disease. The results of this study, published in 1994, showed that dietary protein restriction has a slight beneficial effect upon declining of renal function only among patients with moderate renal insufficiency and blood pressure lowering proved be beneficial only among patients with albuminuria greater than one gram per day[7].

Recently the recognition of phosphorus as an independent risk factor for cardiovascular disease even among non chronic kidney disease patients as well as a risk factor for rapid deterioration of renal function among non dialysis patients and experimental animals put the set of investigation in another direction independent of protein diet and energy consumption[8,9]. It is believed that in CKD the increased reabsorption of filtered phosphate in proximal tubules forms calcium-phosphate crystals, which precipitates in tubular cells mitochondria, interstitium and capillaries aggravating renal damage known as the "precipitation-calcification hypothesis"[10]. More over the recent discovery of the critical role of FGF-23 and *klotho* protein in phosphate homeostasis[(11)] indicate toward the possibility that inorganic phosphate may be a toxic element for our vessels, our heart and our kidneys[9].

Chronic kidney disease: the problem of "timely initiation" of diet and adequate energy intake

Evaluation of LPDs in slowing the deterioration of renal function in chronic kidney disease exhibits a lot of difficulties. First of all recruit of subjects encompass diverse age groups with various degrees of renal failure. The etiology of renal failure is not uniform and the commencement of dietary intervention is probably too late in contrast with experimental animals where the protein restriction is applied immediately after the establishment of renal damage. The compliance of patients restricting the daily protein intake is poor and in the majority of trials the amount of protein ingested is greater than that prescribed. Even more if supplemental ketoacids-amino acids are prescribed there is a considerable difficulty in providing these products and the deleciousness of diets is an additive trouble. Another problem is the sufficient amount of daily energy intake in terms of calories in order to avoid malnutrition[12].

The merely disappointing results of MDRD study misinterpreted from the majority of physicians as failure of diet in slowing the deterioration of renal function in CKD. Careful interpretation of the results showed that patients with glomerular filtration rate of about 40 ml/min showed a GFR reduction of only 3 ml/min per year. This finding means that if it was possible to commence dietary protein restriction and optimal blood pressure control from the inception of disease these patients would need about 20 to 30 years to achieve a GFR of 40 ml/min plus an additional time interval to the end stage of renal failure.It is obvious that the majority of these patients could not be alive then because of an advanced age[13,14]

Further analysis of the MDRD study results showed that the very low protein diets (0,28 g/kg/day) with or without supplemental ketoacids – amino acids did not offer any significant advantage to the low protein diets (0,6 g/kg/day). Patients compliance with low and very low protein diets was unsatisfactory achieving an estimated protein intake of about 0,73 - 0,77 g/kg/day in LPDs and 0,48 g/kg/day in very low protein diets. The daily amount of phosphorus intake was estimated to be at the level of 16-20 mg/kg/day in usual diet, 5-10 mg/kg/day in LPDs and 4-9 mg/kg/day in very low protein diets. Although LPDs showed only a marginal effect upon declining of

renal function compared to the usual protein diets (1,3 g/kg/day) the LPDs consuming patients showed a reduction in uremic symptoms and a much lower GFR at the beginning of haemodialysis or transplantation. The results of MDRD study as well as newly published data showed that LPDs are well tolerated, effective in achieving better metabolic control with fewer drug requirement without evidence of malnutrition[14,15].

Participants in MDRD study were non-diabetic patients.There is scant literature concerning the effect of LPD diets among diabetics type I or II with CKD. Recently a meta-analysis of eight RCTs comparing the results of LPDs in 519 diabetic patients, either type I or II, and various degrees of CKD, showed no significant effect of LPDs upon decline of GFR or creatinine clearance, while a significant effect upon lowering of HbA1c and albuminuria was found[16]. The editorial comment by Kopple JD upon this meta-analysis emphasizes the limitations of RCTs among diabetic patients because of the poor compliance in LPDs, the rationale of treating these patients with ACEIs or ARBs and the recent implementation of high-protein low carbohydrate diets among diabetics before the establishment of kidney disease. The editor conclude that although there is no convincing evidence of beneficial effect of LPDs upon evolution of diabetic nephropathy he advice the use of low protein diets in these patients and according to his experience a proportion of about 15 % of patients are capable to accept conveniently LPDs[17].

According to the United States Renal Data System (USRDS) 11 % of new patients achieving end stage renal disease are older than 70 years of age and the mortality rate in the first year is 35 %, while the mortality rate among patients older than 80 years of age exceeds 50 % the first year after initiation of dialysis[18]. More recently a survey of functional status of elderly patients initiating dialysis therapy in US showed that among 3,577 residents of nursing home, mean age 73,4 ± 10,9 years, the cumulative mortality rate was 58 % at 12 months and only 13 % retained their functional status the remainder 87 % had died or worsening their functional status[19]. On the other hand in a letter to the editor Jassal SV et all reported similar results among their patients initiating haemodialysis or peritoneal dialysis[20]. After that it is questionable whether it is better to maintain these patients in a low protein diet and a rigorous effort of rehabilitation or to initiate substitution of renal function either with dialysis or peritoneal dialysis. The results from the Diet or Dialysis in the Elderly (DODE) study, on behalf of the National Health System of Italy, proved the safety and efficacy of supplemented very low protein diet in postponing dialysis for a median of 12 months among patients older than 70 years of age and GFR levels 5 - 7ml/min[21]. Further analysis of the cost benefit of this study showed a considerable reduction in expenditures at the level of 21,180 €/patient for the first year, 6,500 €/patient for the second year and 682 €/patient for the third year[22].

Diets in Chronic Renal Disease: low protein or low phosphate?

The role of dietary phosphorus intake in the progression of CKD was assessed as early as 1978 by Ibels et al in experimental animals. These investigators showed the beneficial effect of low phosphate diet upon evolution of renal damage in remnant nephrons among 7/8 nephrectomized rats[23]. Two years later Haut LL et al conducted a well controlled trial in rats and showed that increased phosphorus intake is coupled with considerable nephrotoxicity which can be avoided by dietary phosphorus restriction or administration of phosphate binders by means of reducing the amount of phosphate filtered in renal tubules. The main histological finding was the deposition of calcium phosphate in renal tubules and concluded that tubular calcification was the result of increased phosphate excretion per functional renal unit rather than blood phosphate level[24].

Soon there after Maschio et al and Barsotti et al reported their results upon the beneficial effect of low-protein and low-phosphate diets on the progression of renal failure among patients with CKD[25,26]. Based upon cumulated data Kai Lau expressed the "precipitation-calcification hypothesis" as the main mechanism of renal damage by phosphorus. According to this hypothesis, the filtered load of phosphorus per renal tubule increases, as a consequence of increased blood phosphate level and increased snGFR, leading in an increased tubular lumen phosphorus burden and concomitant transepithelial phosphate traffic. In case of CKD the concomitant increase of PTH level leads to increased calcium filtration and reabsorption, which leads to calcium phosphate crystal formation precipitated in epithelial cells and peritubular space with resultant inflammation and fibrosis. Thus any effort to decrease the burden of phosphorus filtered in urine is of outmost importance in alleviating the perpetuation of renal damage in CKD[10].

The mere effect of phosphorus upon evolution of renal damage is difficult to be assessed because the reduction in phosphate intake is coupled with reduction in protein intake and so the interplay of these tow measures in ameliorating renal damage can't be avoided. Kusano K et al investigated the effect of various diets containing graded amount of protein and phosphorus in irreversible Thy 1 rats (experimental animals similar to IgA nephropathy). They applied six isocaloric diets containing 16,9 %, 12,6 % and 8,4 % protein supplemented with either 0,5 % or 0,3 % phosphorus, respectively. The results showed that among usual phosphate diets (0,5 %) only the very low-protein diet (8,4 % protein) had a protective effect upon deterioration of renal function. On the contrary all low-phosphate diets (0,3 %), irrespective of protein content, exhibited a protective effect upon declining of renal function and more importantly they showed that low-phosphate diets were coupled with low PTH levels[27].

Upon clinical grounds the results of PREPARE study showed that phosphate levels among 448 pre-dialysis patients (kidney disease stage IV-V) was inversely corre-

lated with the decline of renal function and mortality rate of these patients[8]. Each mg/dl phosphate increment was associated with an increase in loss of renal function by 0,154 ml/min/month (95 % CI : 0,071 – 0,237) and an increase in mortality risk by 1,25 (95 % CI : 1,02 – 2,59). In another study Kestenbaum B et all examined a cohort of 3490 patients with CKD, from the Veterans Affairs Medical Centers, and found a positive correlation between phosphorus levels and myocardial infarction (MI) and death. The detailed results of this study showed that each mg/dl increment in phosphorus level produced a 35 % increase in the risk for MI (HR 1,35; 95 % CI : 1,09 – 1,66) and a 28 % increase in the risk for death plus nonfatal MI (HR 1,28; 95 % CI : 1,16 – 1,4). More importantly these investigators found that the cutoff point of phosphorus level which produced a statistically significant increase in the risk of death was 3,5 mg/dl[28]. Take in account that K/DOQI guidelines concerning the target for phosphorus levels in CKD stage III - IV are recommend to be lower than 4,6 mg/dl and the daily amount of dietary phosphorus should be restricted to 800 – 1000 mg/day it seems likely that a revision of guidelines may be needed in the view of later findings concerning the toxic effect of phosphorus upon heart and the kidney.

The mechanism by which phosphate burden produces nephrotoxicity and cardiotoxicity is until now obscure but, it seems likely that the precipitation-calcification hypothesis is sufficient to explain the vascular and interstitial matrix calcification of the kidney as well as calcification of coronary arteries and cardiac muscle fibrosis. Moreover experimental studies showed that increased phosphorus concentration is capable to produce transformation of vascular smooth muscle cells to bone forming cells[9]. In case of CKD, reduction of GFR under 60 ml/min/1,73m^2, phosphate levels produce an increase in PTH levels and a decrease in 1,25$(OH)_2$D levels. It is well known that increased PTH levels are consisted with cardiac hypertrophy and an increase in the risk for cardiovascular and all causes mortality[28]. On the other hand a decrease in 1,25$(OH)_2$D levels has shown to be correlated with coronary artery calcification even among patients without CKD[29].

Under the light of recent discoveries it is possible that the common link between all these abnormalities is the FGF23 and klotho protein[11]. FGF23 is a potent phosphaturic substance which inhibits the sodium-phosphate cotransporter in proximal tubules and produces hypophosphatemia in experimental animals and humans.It is also a potent suppressor of 1,25$(OH)_2$D synthesis by inhibiting the 1a-hydroxylase which converts 25 (OH)D to 1,25$(OH)_2$D.In order FGF23 to exert it's phosphaturic action in the kidneys needs the presence of klotho protein, an anti-aging protein, as a cofactor. It is possible that in early stages of CKD the increased burden of phosphate produces an increase in FGF23 production in order to increase phosphate clearance from the kidneys but concomitantly decreases the production of 1,25$(OH)_2$D in an attempt to normalize the phosphate levels. This goal is achieved only in the early stages of CKD but as renal function declines it is impossible to counteract the increased phosphate burden as a consequence of very low number of functioning nephrons and the blood phosphate levels increase with a consequent increase of PTH levels[30]. The above defined alterations describe the full blown picture of secondary hyperparathyroidism, renal osteodystrophy, vascular and soft tissue calcification and heart damage which accompanies the evolution of CKD.

It is obvious that the restriction of phosphate burden in patients with CKD, and not only, is of outmost importance in alleviating renal damage and the accompanying disorders of other organ's function.There is one more problem appearing from the content of food phosphorus by means of the additives used by manufacturers and providers of commonly used foods. Increasing evidence suggest that beyond the amount of phosphorus contained in low-protein diets there is an additional phosphorus quantity ingested by patients with the food additives such as disodium phosphate, monosodium phosphate, potassium triphosphate, sodium acid phosphate, sodium hexamethaphosphate, sodium tripolyphosphate, tetrasodium pyrophosphate and trisodium triphosphate. This amount has been estimated to be as much as 25 – 50 % of the recommended daily intake of phosphorus by diet and more importantly phosphorus contained in additives is 100 % absorbable in contrast to that contained in natural food[31].

After that it is worthy to suggest that another prospective study is needed with special emphasis not only to the amount of protein content in diet but also to the phosphorous and especially to the amount of phosphate additives because it is a real problem not only for CKD patients but also for public health.

References

1. Wasserstein AG. . Changing patterns of medical practice: protein restriction for chronic renal failure. Ann Intern Med 1993; 119: 79-85.
2. Giordano C. Protein restriction in chronic renal failure. (Nephrology Forum). Kidney Int 1982; 22: 401-408.
3. Newburgh LH, Johnston MW. High nitrogen diets and renal injury. The dependence of the injury upon the nature of the nitrogenous substance. J Clin Invest 1931; 10: 153-160.
4. MacKay LL, Addis T, MacKay EM. The degree of compensatory renal hypertrophy following unilateral nephrectomy. The influence of the protein intake. J Exp Med 1938; 67: 515-519.
5. Shimamura T, Morrison AB. A progressive glomerulosclerosis occurring in partial five sixths nephrectomized rats. Am J Path 1975; 79: 95-106.
6. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM.. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981; 241: F85-F93.
7. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. For the Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; 330: 877-884.
8. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW and the PREPARE study group. High plasma phos-

phate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant 2007; 22: 2909-2916.
9. Kanbay M, Goldsmith D, Akcay A, Covic A. . Phosphate – The silent stealthy cardiorenal culprit in all stages of chronic renal disease. Blood Purif 2009; 27: 220-230.
10. Lau K. Phosphate excess and progressive renal failure: the precipitation-calcification hypothesis. Kidney Int 1989; 36: 918-937.
11. Komaba H, Fukagawa M. FGF23: a key player in mineral and bone disorder in CKD. Nefrologia 2009; 29: 392-396.
12. Mehrotra R, Nolph KD. Treatment of advanced renal failure: low-protein diets or timely initiation of dialysis? Kidney Int 2000; 58: 1381-1388.
13. Narins RG, Cortes P . The role of dietary protein restriction in progressive azotemia. N Engl. J Med 1994; 330: 929-930.
14. Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. For the Modification of Diet in Renal Disease (MDRD) study group. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? J Am Soc Nephrol 1999; 10: 2426-2439.
15. Cianciaruso B, Pota A, Pisani A, Torraca S, Annecchini R, Lombardi P, Capuano A, Nazzaro P, Bellizzi V, Sabbatini M. Metabolic effects of two low protein diaets in chronic kidney disease stage 4-5 - a randomized controlled trial. Nephrol Dial transplant 2007; 23: 636-644.
16. Pan Y, Guo LL, Jin HM . Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008; 88: 660-666.
17. Kopple JD. Do low-protein diets retard the loss of kidney function in patients with diabetic nephropathy? Am J Clin Nutr 2008; 88: 593-594.
18. Collins AJ, Kasiske B, Herzog C et all. Experts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis 2005; 45: S1-280.
19. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloth CE. Functional status of elderly adults before and after initiation of dialysis. N Engl J Med 2009; 361: 1539-1547.
20. Jassal SV, Chiu E, Hladunewich M. Loss of independence in patients starting dialysis at 80 years of age or older. N Engl J Med 2009; 361: 1612-1613.
21. Brunori G, Viola BF, Parrinelo G, De Biase V, Como G, Franco V, Gariboto G, Zubani R, Cancarini GC. (2007). Efficacy and safety of a very-low-protein diet when postponing dialysis in elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 2007; 49: 569-580.
22. Scalone L, Borghetti F, Brunori G, Viola BF, Brancati B, Sottini L, Mantovani LG, Cancarini G. Cost-benefit analysis of supplemented very-low protein diet versus dialysis in elderly CKD5 patients. Nephrol Dial Transplant 2010; 25: 907-913.
23. Ibels LS, Alfrey AC, Haut L, Huffer WE. Prevention of function in experimental renal disease by dietary restriction of phosphate. N Engl J Med 1978; 298: 122-126.
24. Haut LL, Alfrey AC, Guggenheim S, Buddington B, Schrier N. Renal toxicity of phosphate in rats. Kidney Int 1980; 17: 722-731.
25. Maschio G, Oldritzzi L, Tessitore N, D' Angelo A, Valvo E, Lupo A, Loschiavo C, Fabris A, Gammaro L, Rugiu C, Panzetta G. Effects of dietary protein and phosphorus restriction on the progression of early reanal failure. Kidney Int 1982; 22: 371-376.
26. Barsotti G, Morelli E, Giannoni A, Guiducci A, Lupetti S, Giovannetti S. Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. Kidney Int 1983; 16: S278-S284.
27. Kusano K, Segawa H, Ohnisi R, Fukushima N, Miyamoto K. Role of low protein diet in the progression of chronic kidney disease in uremic rats. J Nutr Sci Vitaminol 2008; 54: 237-243.
28. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress D. Serum phosphate levls and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005; 16: 520-528.
29. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997; 96: 1755-1760.
30. Fukagawa M, Kazama J. With or without the kidney: the role of FGF23 in CKD. Nephrol Dial transplant 2005; 20: 1295-1298.
31. Sigrist MK, Chiarelli G, Lim L, Levin A. (2009). Early initiation of phosphate lowering dietary therapy in non-dialysis chronic kidney disease: a critical review. J Ren Care 2009; 35: S71-S78.