ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 4, Issue – 1, January - February - 2021, Page No. : 180 – 189

Epidemiology of Low-Proteinuric Chronic Kidney Disease in Renal Clinics

[1]Dr Mujtaba Ali Hasnain, Consultant Nephrologist, Assistant Professor of Medicine, Capital District Renal Physicians, Albany Medical College, Albany, New York, USA.

[2]Dr Muhammad Shahzad Gul, Nephrology Department, Mayo hospital.

[3]Dr Hafiz Muhammad Sajid Anayat, Allied hospital, Faisalabad

[4]Dr Muhammad Usman Yoosuf, Jinnah Hospital, Lahore

[2]Dr Javaria Karamat, Sheikh Zayed Hospital, Lahore

[6]Dr. Samrah Mujtaba, Capital District Renal Physicians, Albany, New York, USA.

Corresponding Author: Dr Mujtaba Ali Hasnain, Consultant Nephrologist, Assistant Professor of Medicine, Capital District Renal Physicians, Albany Medical College Albany New York USA.

How to citation this article: Dr Mujtaba Ali Hasnain, Dr Muhammad Shahzad Gul , Dr Hafiz Muhammad Sajid Anayat, Dr Muhammad Usman Yoosuf, Dr javaria karamat, Dr. Samrah Mujtaba,“ Epidemiology of Low-Proteinuric Chronic Kidney Disease in Renal Clinics”, IJMACR- January - February - 2021, Vol – 4, Issue -1, P. No. 180 – 189.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Chronic kidney disease patients with low-grade proteinuria (LP) are common in nephrology clinics. However, prevalence, characteristics, and the competing risks of chronic kidney disease and death as the specific determinants, are still unknown. Modifiable risk factors were also different in low-grade proteinuria, with smoking, lower hemoglobin, and proteinuria being associated with higher mortality risk while lower BMI and higher phosphorus predicting kidney disease. Therefore, in nephrology clinics, low-grade proteinuria patients are the majority and show distinctive basal features. More important, they are more exposed to death than chronic kidney disease and do present specific modifiable determinants of either outcome indeed, in low-grade proteinuria, while smoking plays a role for mortality, lower basal metabolic index and higher phosphorus levels -even if in the normal range- are predictors of chronic kidney disease. These data support the need to further study the low proteinuric chronic kidney disease population to guide management.

Keywords: ND-CKD, LP, Diabetes, Itching

Introduction

In current nephrology practice, a limited number of nephrologists must cope with the growing population of non-dialysis chronic kidney disease (ND-CKD) patients characterized by advanced disease and higher burden of comorbidities requiring watchful and time-consuming care.[1] Therefore, optimizing risk stratification in this clinical setting becomes of paramount importance because

it allows to properly individualize clinical management in terms of monitoring as treatment. Previous analyses have demonstrated that in non-dialysis chronic kidney disease proteinuria is a major risk factor of cardiorenal outcome besides and beyond age, chronic kidney disease stage and type of primary renal disease.[2-9] Indeed, the most recent Kidney Disease: Improving Global Outcomes clinical practice guidelines for the evaluation and management of chronic kidney disease have identified the proteinuria level of 0.5 g/24h as a meaningful threshold to define chronic kidney disease severity in general and high-risk populations.[10] However, outcome and risk factors of chronic kidney disease patients with low-grade proteinuria, that is, less than 0.5 g/24h,that are regularly followed in renal clinics are still undefined. Interest on this issue is remarkable because cross-sectional studies, in the general population as in different clinical settings, have shown that low-proteinuric patients are common.[11-16] In particular, a recent cross-sectional analysis of basal features of non-dialysis chronic kidney disease patients under nephrology care has evidenced that these patients are the majority of chronic kidney disease population with low grade.[16] Nevertheless, no prognostic information for the low-proteinuric condition in nephrology clinics, as for other clinical settings, have been provided so far. To fill this important gap of knowledge, we studied a large population of low-proteinuric patients with non-dialysis chronic kidney disease stage III-V under stable nephrology care to evaluate their epidemiologic features, and prognosis in terms of risks of end-stage renal disease (ESRD) and all-cause mortality as the specific determinants of either outcome. Patients with proteinuria higher than 0.5 g/24h constituted the control group. Noteworthy, survival analyses accounted for the underlying renal disease, that mainly influences the degree of proteinuria and outcome as well, and for the competing nature of the risk of end stage renal disease and mortality.[17] This latter point is critical; competing risk analysis in fact allows to estimate the “full” effect of risk factors for chronic kidney disease progression because many non-dialysis chronic kidney disease patients do not reach end stage renal disease as they die before.[2-9] Results provide useful information to identify potential therapeutic targets and design future trials in low-proteinuric chronic kidney disease.

Anyone can get chronic kidney disease. Some people are more at risk than others. Some things that increase your risk for chronic kidney disease include:

- Diabetes
- High blood pressure (hypertension)
- Heart disease
- Having a family member with kidney disease
- Being African-American, Hispanic, Native American or Asian
- Being over 60 years old

Symptoms of Kidney Failure

- Itching
- Muscle cramps
- Nausea and vomiting
- Not feeling hungry
- Swelling in your feet and ankles
- Too much urine (pee) or not enough urine
- Trouble catching your breath
- Trouble sleeping

If your kidneys stop working suddenly (acute kidney failure), you may notice one or more of the following symptoms:

- Abdominal (belly) pain
- Back pain
- Diarrhea
- Fever
- Nosebleeds

- Rash
- Vomiting

Your kidneys help your whole body work properly. When you have chronic kidney disease, you can also have problems with how the rest of your body is working. Some of the common complications of chronic kidney disease include gout, anemia, bone disease, heart disease, high potassium, high calcium and fluid buildup.

- Gout
- Anemia
- Metabolic acidosis
- Bone disease and high phosphorus (hyperphosphatemia)
- Heart disease
- High potassium (hyperkalemia)
- Fluid buildup

Gout

Most commonly, kidney disease can cause gout. However, gout may also lead to kidney disease. Since uric acid is filtered through the kidneys, the two diseases are related.

Anemia

Your kidneys help your body make red blood cells. When your kidneys are not working properly, your body may not have enough red blood cells. This condition is called anemia.

Metabolic Acidosis

Metabolic acidosis is a buildup of acid in your body. Your kidneys help keep the right balance of acids in your body. Metabolic acidosis is common in people with kidney disease because their kidneys are not filtering their blood well enough.

Bone Disease and High Phosphorus (Hyperphosphatemia)

You need calcium and vitamin D to have healthy bones. Healthy kidneys help keep your bones healthy. If you have chronic kidney disease, your kidneys may not be able to do this important job.

Heart Disease

Heart disease can cause kidney disease, but kidney disease can also cause heart disease. Heart disease is the most common cause of death among people on dialysis.When your kidneys are not working well, they cannot support the other parts of your body as they should. This can cause problems with your heart.

High Potassium (Hyperkalemia)

Healthy kidneys filter extra potassium (a mineral found in many foods) from the blood. If you have chronic kidney disease, you need to limit your potassium because your kidneys may not be able to filter it.

Fluid Buildup

Healthy kidneys take out extra fluid (liquid) from your blood. When your kidneys are not working as well as they should, they cannot take out enough fluid. This can cause the extra fluid in your blood to build up in your body. Having too much fluid in your body can cause problems with your heart and lungs. It can also cause high blood pressure, which is the second most common cause of kidney failure. Controlling your fluid intake can help prevent these problems and lower your risk for further kidney damage. If your body is holding on to too much fluid, you may notice a faster heartbeat and swelling that starts in your feet and ankles and moves upward. Limiting how much fluid you take in can help you feel better.

Use these tips to limit how much fluid you take in each day and remain hydrated

- Follow a low-salt diet. Salt can make your body hold on to more fluid than it should.
- If you are thirsty, try sucking on an ice cube or a hard candy (sugar-free if you have diabetes).
- Remember that foods, such as ice cream and soup, count as fluid. Fruits and vegetables also have fluid

in them. Each time you eat or drink something that is considered a fluid, write it down. Keep track of how much fluid you take in throughout the day.

Causes of Chronic Kidney Disease

Chronic kidney disease is usually caused by other conditions that put a strain on the kidneys. Often it's the result of a combination of different problems.

Chronic kidney disease can be caused by:

- high blood pressure – over time, this can put strain on the small blood vessels in the kidneys and stop the kidneys working properly
- diabetes – too much glucose in your blood can damage the tiny filters in the kidneys
- high cholesterol – this can cause a build-up of fatty deposits in the blood vessels supplying your kidneys, which can make it harder for them to work properly
- kidney infections
- glomerulonephritis – kidney inflammation
- polycystic kidney disease – an inherited condition where growths called cysts develop in the kidneys
- blockages in the flow of urine – for example, from kidney stones that keep coming back, or an enlarged prostate
- long-term, regular use of certain medicines – such as lithium and non-steroidal anti-inflammatory drugs (NSAIDs)

Tests for Chronic Kidney Disease

Chronic kidney disease can be diagnosed using blood and urine tests. These tests look for high levels of certain substances in your blood and urine that are signs your kidneys aren't working properly. If you're at a high risk of developing kidney disease (for example, you have a known risk factor such as high blood pressure or diabetes), you may be advised to have regular tests to check for chronic kidney disease so it's found at an early stage. The results of your blood and urine tests can be used to tell the stage of your kidney disease. This is a number that reflects how severe the damage to your kidneys is, with a higher number indicating more serious chronic kidney disease.

Treatments for Chronic Kidney Disease

There's no cure for chronic kidney disease, but treatment can help relieve the symptoms and stop it getting worse. Your treatment will depend on how severe your condition is. The main treatments are:

- lifestyle changes to help you remain as healthy as possible
- medicine to control associated problems such as high blood pressure and high cholesterol
- dialysis – treatment to replicate some of the kidney's functions; this may be necessary in advanced chronic kidney disease
- kidney transplant – this may also be necessary in advanced chronic kidney disease

You'll also be advised to have regular check-ups to monitor your condition.

Outlook for Chronic Kidney Disease

Chronic kidney disease can range from a mild condition with no or few symptoms, to a very serious condition where the kidneys stop working, sometimes called kidney failure. Most people with CKD will be able to control their condition with medicine and regular check-ups. CKD only progresses to kidney failure in around 1 in 50 people with the condition.If you have chronic kidney disease, even if it's mild, you're at an increased risk of developing other serious problems, such as cardiovascular disease. This is a group of conditions affecting the heart and blood vessels, which includes heart attack and stroke. Cardiovascular disease is one of the main causes of death in people with kidney disease, although healthy lifestyle changes and medicine can help reduce your risk of developing it.

Method

Study Design: This is an observational study examining 2,340 patients with non-dialysis chronic kidney disease stage III-V enrolled in three established prospective cohorts of non-dialysis chronic kidney disease patients.[5,8,18] The three cohorts were originally built to collect prospective epidemiologic information on consecutive chronic kidney disease patients under regular care in nephrology clinics. Cohorts shared the main inclusion (established diagnosis of chronic kidney disease and first visit dating back more than 6 months before baseline) and exclusion criteria (renal replacement therapy, acute kidney injury, active malignancy). After pooling the data, we excluded duplicate subjects and those with chronic kidney disease stage I-II or with missing values of covariates included in survival analyses. For the specific purposes of the present study, we stratified patients in two groups: low-proteinuric (LP) group, including patients with basal proteinuria level0.5 g/24h and control group, constituted by those with basal proteinuria >0.5 g/24h. The 0.5 level was chosen according to the new classification of chronic kidney disease that identifies patients with proteinuria above this threshold as having “severe chronic kidney disease”.[10] We did not select the 0.150 g/24 value to separate the two groups because this threshold, defining normality of protein excretion, may be more appropriate in general population than in our patients with overt chronic kidney disease, under long term Nephrology care and treated with antiproteinuric polytherapy.

Procedures

As for selection criteria, procedures did not differ in the three studies. Participating nephrologists collected information, including diagnosis of underlying renal disease, history of cardiovascular (CV) disease, that is, any documented event among myocardial infarction, stroke, angina pectoris, heart failure, peripheral vascular disease. Nephrologists performed the physical examination with assessment of height, body weight, blood pressure (BP), and registered lab results and therapy. Data were collected in anonymous electronic case reports subsequently sent to the coordinating center for analyses. The classification in two groups was made on the basis of the proteinuria level registered at the first available visit after at least six months of follow up in the Nephrology clinic. That visit represents the baseline visit in the present study. In the three cohorts, laboratory protocols were standardized with in-house analyses. 24-hour urine collection was obtained to quantify proteinuria and evaluate adherence to the prescribed restriction of protein and salt intake; collection was considered inaccurate, and repeated, if creatinine excretion was outside of the 60 to 140% range of the value calculated.[19] Patients that likely have true chronic kidney disease, as suggested by the prolonged and continuous nephrology follow up. The importance of the clinical setting is supported by the comparison of prognosis in our study versus early work in general population and or unreferred cohorts. Specifically, the residual risk of progression to end stage renal disease in low proteinuric, though relatively lower when compared to what observed for HP patients, was still relevant in absolute terms. In large studies in general population,[20,21] in fact, the mean incidence rate of end stage renal disease ranged from 0.004 to 0.1/100 subject-y, a 30- to 700-fold lower rate than what recorded in lowproteinuric patients (2.7/ 100 pt-y). Finally, chronic kidney disease patients exclusively followed in the primary care setting, and with age and eGFR similar to our referred lowproteinuric group,[22] had a 10-fold lower end stage renal disease incidence (0.25/100 pt-y).

Overall, these data therefore indicate that chronic kidney disease patients are at a relatively higher risk of end stage renal disease even after a prolonged nephrology care and even in the presence of low proteinuria. Interestingly, the two groups showed similar cardiovascular risk (fatal and non-fatal cardiovascular events). Reason for this result is not readily apparent; however, it may depend on the fact that the higher cardiovascular risk conveyed by older age in low proteinuric is counterbalanced by the larger prevalence of diabetes, besides and beyond the higher proteinuria in this group that increases cardiovascular risk.[23] Noteworthy, the separate analysis of the two groups also allows to optimize risk profile and discrimination of the risk factors specific to either outcome. Due to the clinical setting of tertiary nephrology care, focusing on risk factors potentially modifiable by therapy becomes particularly important. When examining mortality risk, besides low hemoglobin, that had a significant predictive role in either group, smoking emerged as a major modifiable determinant specific to low proteinuric condition. Low proteinuric patients may be therefore more exposed to the worsening effect of smoking on survival. It is reasonable to hypothesize that this association may relate to the superimposition of smoking,that linked to atheromatosis and vascular calcification, over an ischemic background correlated to the older age and the higher prevalence of hypertensive disease in this group.[24-26]. The remarkable prognostic role of this habit suggests that more time and efforts should be dedicated particularly in these patients for counseling on smoking. Similar to smoking, also the degree of proteinuria predicted mortality in low proteinuric only; this finding may be coherent to the role of low-grade proteinuria as recognized proxy of atherosclerosis-associated vasculopathy.[27]

As observed for mortality risk, the modifiable determinants of renal prognosis differed in low proteinuric. Higher basal metabolic index tells a lower end stage renal disease risk only in this group. It is possible that the renal protective effects of “better” nutritional reserves may be enhanced in low proteinuric due to their distinctive characteristics, older age and a pro-atherosclerotic.[28] Indeed, a recent large study in general population has shown that moderately increased basal metabolic index prevalent feature in our population protects against loss of renal function in older patients.[29] An original finding, of great clinical relevance, is the linkage between phosphorus and proteinuria on renal prognosis. Phosphorus emerged as the main modifiable determinant of end stage renal disease in low proteinuric. This role persisted also in patients although the association of phosphorus and risk of end stage renal disease was significantly attenuated in the presence of higher levels of proteinuria. Relevance of these observations increases when considering that phosphorus levels, normal in the vast majority of cohort, were significantly lower in low proteinuric. This difference is mainly due to the higher eGFR in low proteinuric; however, we cannot exclude the contribution of a lower tubular reabsorption of phosphorus linked to the low proteinuria in this group, as recently suggested by an experimental study.[30] The interaction between phosphorus and proteinuria on renal risk adds novel insights into the critical -and so far still unsolved- issue of the definition of the optimal phosphorus levels in non-dialysis chronic kidney disease.[31,32] Indeed, while previous studies have collectively evidenced that P levels, even in the normal range, predict progression to ESRD,[33] data obtained in more than 10,000 chronic kidney disease patients with eGFR <60 ml/min per 1.73m2 confute this independent association.[34] Our results suggest that the

predictive role of P on renal outcome is strongly influenced by the entity of proteinuria.

In this regard, two hypotheses can be made. The first is merely related to the potential limitations intrinsic to all survival analyses, that is, the strength of an association between exposure to a given risk factor (proteinuria) and outcome end stage renal disease may be so high to attenuate the role of other risk factors (phosphorus). The second is more based on pathophysiology; indeed, the causative role of phosphorus on chronic kidney disease progression, which is mainly mediated by tubulo-interstitial fibrosis similarly to proteinuria,[35,36] may be greater if the proteinuria-induced renal injury is less evident. This latter hypothesis is supported by the evidence that the nephroprotective effects of antiproteinuric therapy increases when phosphorus levels are low.[37,38] Interestingly, the two groups shared a higher end stage renal disease risk in diagnosis of primary renal disease. This observation suggests that, at least so far, this specific renal disease suffers of the paucity of effective therapeutic tools with respect to other renal diseases. Indeed, in a recent study by our group, we found that after intensification of therapy during first year of Nephrology care in chronic kidney disease patients, risk of end stage renal disease decreased in all renal diseases.[8] Our study is limited by the assessment of predictors only at baseline; nevertheless, the prolonged follow up in nephrology prior to basal visit 12 months on average reasonably excludes substantial changes of risk factors in the subsequent period. Furthermore, our analysis does not allow to distinguish patients who reverted from high proteinuria status from those with proteinuria persistently low; however, the study was designed to evaluate low proteinuric with the aim of refining risk stratification after long-standing nephrology care. Finally, analyses of factors associated with end stage renal disease .On the other hand, the study has strengths such as the size of population, which is relatively large when considering the referral status of patients, as well as the fact that survival analyses were adjusted for several factors, including the renal diagnoses which in many population based cohorts is not the case.

Conclusion

This study provides novel information on the non-dialysis chronic kidney disease population under regular nephrology care. We found that low proteinuric patients are the majority and show distinctive basal features. More important, they are more exposed to death than end stage renal disease and do present differences in the modifiable determinants of either outcome; indeed, while smoking plays a role for mortality, lower BMI and higher phosphorus levels -even if in the normal range- are predictors of end stage renal disease. These data extend to the population of patients regularly followed in nephrology the clinical relevance of the 0.5 g/24h proteinuria threshold,that has been indicated by the new guidelines as a simple marker to stratify the risk in the general non-dialysis chronic kidney disease population. Overall, these data support the need to further study the low proteinuric chronic kidney disease population to guide management.

References

1. Bello AK, Levin A, Manns BJ, Feehally J, Drueke T, Faruque L, et al. Effective CKD care in European countries: challenges and opportunities for health policy. Am J Kidney Dis. 2015; 65(1):15–25.
2. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis. 2008; 52(4): 661–671.

3. Obi Y, Kimura T, Nagasawa Y, Yamamoto R, Yasuda K, Sasaki K, et al. Impact of age and overt proteinuria on outcomes of stage 3 to 5 chronic kidney disease in a referred cohort. Clin J Am Soc Nephrol. 2010; 5(9):1558–1565.
4. Hoefield RA, Kalra PA, Baker P, Lane B, New JP, O'Donoghue DJ, et al. Factors associated with kidney disease progression and mortality in a referred CKD population. Am J Kidney Dis 2010; 56: 1072– 1081.
5. De Nicola L, Chiodini P, Zoccali C, Borrelli S, Cianciaruso B, Di Iorio B, et al.; SIN-TABLE CKD Study Group. Prognosis of CKD patients receiving outpatient nephrology care in Italy. Clin J Am Soc Nephrol 2011; 6(10): 2421–2428.
6. De Nicola L, Minutolo R, Chiodini P, Borrelli S, Zoccali C, Postorino M, et al.; SIN-TABLE CKD Study Group. The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care. Kidney Int. 2012 Aug; 82(4):482–8.
7. Sud M, Tangri N, Levin A, Pintilie M, Levey AS, Naimark DM. CKD stage at nephrology referral and factors influencing the risks of ESRD and death. Am J Kidney Dis. 2014 Jun; 63(6):928–36.
8. De Nicola L, Provenzano M, Chiodini P, Borrelli S, Garofalo C, Pacilio M, et al. Independent Role of Underlying Kidney Disease on Renal Prognosis of Patients with ChronicKidney Disease under Nephrology Care. PLoS One. 2015; 10(5):e012707.
9. Haynes R, Staplin N, Emberson J, Herrington WG, Tomson C, Agodoa L, et al. SHARP Collaborative Group. Evaluating the Contribution of the Cause of Kidney Disease to Prognosis in CKD: Results From the Study of Heart and Renal Protection (SHARP). Am J Kidney Dis 2014; 64:40–8.
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Clinical practice guideline for the evaluation and management of Chronic Kidney Disease. Kidney Int Suppl 2013;
11. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, et al.; for the Chronic Kidney Disease Prognosis Consortium. Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012; 308(22):2349–2360.
12. Zhang L, Wang F, Wang L, Liu B, Liu J, Chen M, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012; 379(9818):815–822.
13. Mottl AK, Kwon KS, Mauer M, Mayer-Davis EJ, Hogan SL, Kshirsagar AV. Normoalbuminuric diabetic kidney disease in the U.S. population. J Diabetes Complications. 2013; 27(2):123–7.
14. De Nicola L, Donfrancesco C, Minutolo R, Lo Noce C, Palmieri L, De Curtis A, et al.; for CARHES Study Group. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008– 12 National Health Examination Survey. Nephrol Dial Transplant. 2015; 30(5):806–814.
15. Porrini E, Ruggenenti P, Mogensen CE, Barlovic DP, Praga M, Cruzado JM, et al.; ERA-EDTA diabesity working group. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2015; 3(5):382–91.
16. Titze S, Schmid M, Ko ¨ttgen A, Busch M, Floege J, Wanner C, et al. GCKD study investigators. Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. Nephrol Dial Transplant. 2015; 30(3):441–51.
17. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing

risks methods for survival analysis in nephrology? Nephrol Dial Transplant 2013; 28(11): 2670–2677.

18. Minutolo R, Locatelli F, Gallieni M, Bonofiglio R, Fuiano G, Oldrizzi L, et al.; REport of COmorbidities in non-Dialysis Renal Disease Population in Italy (RECORD-IT) Study Group. Anaemia management in non-dialysis chronic kidney disease (CKD) patients: a multicenter prospective study in renal clinics. Nephrol Dial Transplant. 2013; 28(12):3035–45.
19. Dwyer J, Kenler SR. Assessment of nutritional status in renal disease. In: Mitch WE, Klahr S (eds). Nutrition and the Kidney, 2nd edn Little, Brown and Company: Boston, MA, 1993, pp 61–95.
20. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005; 165(8):923–8.
21. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006; 144(1):21–8.
22. Minutolo R, Lapi F, Chiodini P, Simonetti M, Bianchini E, Pecchioli S, et al. Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study. Clin J Am Soc Nephrol. 2014; 9(9):1586–93.
23. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011 Jul; 80(1):17–28.
24. Betriu A, Martinez-Alonso M, Arcidiacono MV, Cannata-Andia J, Pascual J, Valdivielso JM, et al.; Investigators from the NEFRONA Study. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transplant. 2014; 29(7):1415–22.
25. Go ´rriz JL, Molina P, Cervero ´n MJ, Vila R, Bover J, Nieto J, et al. Vascular calcification in patients with nondialysis CKD over 3 years. Clin J Am Soc Nephrol. 2015; 10(4):654–66.
26. Nakamura K, Nakagawa H, Murakami Y, Kitamura A, Kiyama M, Sakata K, et al.; EPOCH–JAPAN research group. Smoking increases the risk of all-cause and cardiovascular mortality in patients with chronic kidney disease. Kidney Int. 2015; 88(5):1144–52.
27. Rein P, Saely CH, Vonbank A, Fraunberger P, Drexel H. Is albuminuria a myocardial infarction risk equivalent for atherothrombotic events? Atherosclerosis. 2015; 240(1):21–25.
28. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD, et al. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 2007; 10(4):433–442.
29. Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP. Association of age and BMI with kidney function and mortality: a cohort study. Lancet Diabetes Endocrinol. 2015; 3(9):704–14.
30. de Seigneux S, Courbebaisse M, Rutkowski JM, Wilhelm-Bals A, Metzger M, Khodo SN, et al.; NephroTest Study Group. Proteinuria Increases Plasma Phosphate by Altering Its Tubular Handling. J Am Soc Nephrol. 2015; 26(7):1608–18.
31. Bellasi A. Pro: Should phosphate binders be used in chronic kidney disease stage 3–4? Nephrol Dial Transplant. 2016; 31(2):184–188.
32. Kestenbaum B. Con: Phosphate binders in chronic kidney disease. Nephrol Dial Transplant. 2016; 31 (2):189–194.
33. Da J, Xie X, Wolf M, Disthabanchong S, Wang J, Zha Y, et al. Serum Phosphorus and Progression of CKD

and Mortality: A Meta-analysis of Cohort Studies. Am J Kidney Dis. 2015; 66(2):258.

34. Mehrotra R, Peralta CA, Chen SC, Li S, Sachs M, Shah A, et al.; Kidney Early Evaluation Program (KEEP) Investigators. No independent association of serum phosphorus with risk for death or progression to end-stage renal disease in a large screen for chronic kidney disease. Kidney Int. 2013; 84 (5):989–97.
35. Khan SR. Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. Clin Exp Nephrol. 2004; 8(2):75–88.
36. Kuro-o M. Klotho, phosphate and FGF-23 in ageing and disturbed mineral metabolism. Nat Rev Nephrol. 2013; 9(11):650–660.
37. Zoccali C, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G, et al.; REIN Study Group. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. J Am Soc Nephrol 2011; 22(10):1923–1930.
38. Di Iorio BR, Bellizzi V, Bellasi A, Torraca S, D'Arrigo G, Tripepi G, et al. Phosphate attenuates the antiproteinuric effect of very low-protein diet in CKD patients. Nephrol Dial Transplant. 2013; 28(3):632–40.