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BIOMARKERS OF OUTCOMES IN HEMODIALYSIS PATIENTS

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Abstract

Chronic kidney disease is a complex condition, where the decrease in kidney function is accompanied by numerous metabolic changes affecting virtually all the organ systems of the human body. Many of the markers characteristic of the individually affected organ systems have been associated with adverse outcomes in CKD; it is believed that the high mortality seen in CKD is a result of several abnormalities conspiring to induce a heightened degree of morbidity and mortality. Not all the biomarkers may, however, be causally responsible for the adverse outcomes associated with them. We review various biomarkers of protein energy wasting, inflammation, oxidative stress, potassium disarrays, acid-base disorders, bone and mineral disorders, glycemic status, and anemia management. Although all of these biomarkers have shown associations with worsened outcomes in CKD, markers of protein and energy wasting, especially serum albumin, remain the strongest predictor of survival in CKD patients. We also review the putative pathophysiologic mechanisms behind these associations, and present possible therapeutic interventions that could result in remedies to improve poor clinical outcomes in CKD.

Keywords

Protein energy wasting; inflammation; oxidative stress; potassium; acidosis; renal osteodystrophy; hemoglobin A1c; anemia

INTRODUCTION

Patients with ESRD have mortality rates that exceed those seen with most malignancies.[1] Observational studies have linked metabolic changes to increased morbidity and mortality in dialysis patients, but few clinical trials have been conducted to prove a causal link between these risk markers and adverse outcomes. We examined the various biochemical markers

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that have been associated with adverse outcomes in dialysis patients, and analyzed the potential interventions that may improve outcomes in this patient population.

Mineral and bone disorders

Disorders of mineral and bone metabolism occur frequently in CKD[2] and have been associated with increased mortality.[3;4] Observational studies in dialysis patients have linked hyperphosphatemia and the calcium-phosphorus product [3;4] (Figure 1) and secondary hyperparathyroidism (SHPT)[3–7] with higher cardiovascular morbidity and mortality. The mechanism(s) responsible for these adverse outcomes could be phosphorus' calcification-inducing effects,[8;9] or the deleterious effects of SHPT, which in itself is able to induce cardiovascular, metabolic, hematologic and immunologic changes.[10] Vascular calcification was also found to be associated with higher serum calcium,[11–13] and higher serum calcium levels were associated with higher mortality [3;4] in dialysis patients. Due to the lack of clinical trials the choice of the best therapeutic agent for treating the various aspects of CKD-MBD continues to be debated.[14;15]

Markers of anemia

Lower hemoglobin levels have been associated with adverse outcomes in MHD patients in multiple observational studies.[16–19] In clinical studies, moderate increase in hemoglobin concentration is associated with relief from symptoms of anemia and improved quality of life[18;20] and survival.[21] Several recent randomized clinical trials have shown that targeting hemoglobin levels above 13 g/dL to "normalize" hemoglobin in CKD may be associated with poor clinical outcomes.[22–26] A recent retrospective study of 58,058 maintenance hemodialysis patients also demonstrated an inverse J-curve relationship between hemoglobin levels and adverse outcomes,[19] in that hemoglobin levels between 11.5 and 13 g/dl were associated with the lowest death risk. Improved survival outcomes were observed in dialysis patients using erythropoesis stimulating agents (ESA) at any doses, whereas among those who received an ESA, a higher dose requirement was a surrogate of higher death risk, an effect that may be related to the association between ESA responsiveness index (averaged ESA dose divided by averaged hemoglobin within each 3 month) and malnutrition-inflammation complex (Figure 2).[19] Finally, markers of iron status including serum ferritin and iron saturation ratio appear associated with survival in CKD patients,[27] although serum ferritin may also be an inflammatory marker.[28] The field of anemia of CKD is the only one where original observational studies of potential actionable risk factors in MHD were followed up by several large randomized controlled trials in an attempt to prove a causal link between the exposure (anemia) and the outcome (mortality of cardiovascular events).[22–26] Limitations inherent of many observational studies were thereby exposed, as higher hemoglobin targets in clinical trials have resulted in higher, not lower event rates. The reasons behind this are still debated, and include possible deleterious effects related to higher hemoglobin, but also to the higher doses of erythropoetin needed to achieve higher hemoglobin targets.[29–32] The debate has thus been centered not only on what the ideal hemoglobin level should be in MHD, but also on what the ideal treatment(s) for anemia is in these patients, with various novel ESA analogues and iron products making it potentially possible to explore alternative means of reaching the same goal.

Serum potassium

Both hypokalemia[33] and hyperkalemia[33;34] have been associated with higher mortality in patients on hemodialysis. The effect of hypokalemia on mortality appeared to be due to the poor nutritional status associated with this condition in a study of 81,013 patients receiving maintenance hemodialysis.[35] The importance of appropriate dialysate potassium concentrations was emphasized by the higher mortality seen in patients with hyperkalemia who were dialyzed with dialysates of higher, rather than lower potassium concentration.[35]

Protein-energy wasting

Several markers of PEW have been associated with morbidity and mortality in patients on dialysis. Lower serum albumin,[36–39] prealbumin[40–46] and cholesterol[39;47–50] levels (Figure 3) have been associated with higher mortality in dialysis patients. Other biochemical markers that are directly or indirectly linked to PEW and outcomes include serum transferrin,[51;52] creatinine[53;54] and bicarbonate,[55;56] various hormones such as leptin,[57] visfatin,[58] adiponectin,[59] and thyroid hormones.[60] The mechanism of action responsible for the adverse outcomes associated with PEW markers remain unclear; it is likely that a combination of factors are responsible, rather than a single etiologic mechanism.[61] Malnutrition causes impaired immune function leading to heightened susceptibility to infections and poor wound healing.[62] Certain nutrients such as arginine and glutamine may enhance the immune response.[63–65] CKD patients may be susceptible to zinc,[66;67] vitamin B6 (pyridoxine), vitamin C and folic acid deficiencies,[68;69] which can induce alterations in host defense. Levocarnitine may protect against endotoxins and also suppress elaboration of tumor necrosis factor alpha (TNF-α) from monocytes.[70] Loss of adiposity in CKD could result in decreased sequestration of uremic toxins[71] and lower production of anti-inflammatory cytokines and adiponectine.[72] Sarcopenia seen in malnutrition results in reduced skeletal, respiratory and cardiac muscle function, and also in lower muscle oxidative metabolism with consequently decreased antioxidant defense.[73] Damage of muscle cells may cause the emergence of circulating actin that can consume gelsolin (which is in itself primarily produced by skeletal muscle), vitamin D binding protein and other circulating molecules with salutary and protective action.[74–76] The gastrointestinal tract is also adversely affected in malnutrition, with atrophy of the gut lining, decreased intestinal secretions and altered gut flora leading to further reduction in gut function and the ability to absorb nutrients.[77]

Some of the small clinical trials that have shown improvement in various nutritional markers have used oral or parenteral nutritional supplementation,[78–81] anabolic therapies with human growth hormone[82] or testosterone supplementation,[83–85] or daily dialysis.[86;87] A recent randomized controlled trial of nutritional supplementation showed that an increase in prealbumin of >30 mg/L within 3 months predicted a 54% decrease in mortality, reduced hospitalizations and improved general well-being.[88] These results have to be interpreted conservatively, though, since the change in prealbumin was not the primary end point of the study.

Chronic inflammation

Chronic inflammation is one of many non-conventional risk factors that could explain the excess mortality in patients with CKD. Studies have reported a strong association between pro-inflammatory cytokine levels and adverse outcomes in CKD.[52;54;89–91] A possible explanation for this is the involvement of inflammation in the process of atherosclerosis.[92] The complexity of the inflammatory system has allowed the development of various antiinflammatory agents; unfortunately, most of these agents have not been studied in CKD yet, but the future application of some of them appears promising.[93]

Oxidative stress

Markers of oxidative modification of lipids[94;95] and proteins[96;97] are present in increased amounts in patients with CKD. Low intake of dietary antioxidants has been associated with cardiovascular disease in the general population,[98] and various markers of oxidative stress were associated with higher mortality and cardiovascular disease in dialysis patients.[99–102] Small clinical trials in dialysis patients have shown lower cardiovascular event rates with the administration of vitamin E[103] and N-acetylcysteine.[104] Larger trials are needed to confirm these results and to determine if such interventions can decrease mortality.

Metabolic acidosis

In a study examining 56,385 maintenance hemodialysis patients a serum bicarbonate concentration <22 mEq/liter was associated with lower mortality in unadjusted analyses, but with higher mortality after extensive adjustments for markers of malnutrition and inflammation.[56] Lower bicarbonate was associated both with better nutritional status and worse outcomes in two other large observational studies of dialysis patients.[53;55] Treatment of metabolic acidosis by virtue of dialytic therapies is performed routinely, but no clinical trials have examined whether this interventions improves outcomes independent of the other effects of dialysis.

Glucose control

Several studies have examined outcomes associated with glycemic control in dialysis patients.[105–112] A recent large study of 24,875 dialysis patients[109] reported no association between HbA1c levels and mortality. The lack of survival association in this study could have been due to the short duration of follow-up (12 months) and inadequate controlling for malnutrition, inflammation and anemia. This was supported by another study that found a paradoxically lower unadjusted mortality associated with higher HbA1c levels, but adjustment for markers of malnutrition and inflammation resulted in higher HbA1c levels being associated with increased mortality.[113] A single interventional study examined clinical outcomes in 83 dialysis patients undergoing intensive diabetes-related intervention compared to standard care.[107] Patients in the intensive intervention arm experienced improved quality of life and a reduction in the need for amputations and hospitalizations.[107] Establishment of specific blood glucose targets for dialysis patients is important, given that the complex glycemic dysregulation characteristic of the uremic state may make treatment guidelines derived from populations with normal kidney function inappropriate for such patients.[114]

CONCLUSIONS

Many biochemical markers are associated with adverse outcomes in CKD. Some of these represent factors that may be causally related to the adverse outcomes, and others could be merely markers of underlying complex pathophysiologic processes. Some therapeutic interventions in CKD have improved the level of various biomarkers, without definitive evidence for a beneficial effect on hard clinical end points such as mortality. Such effects need to be shown in future clinical trials.

Reference List

1. Kalantar-Zadeh K, Abbott KC, Kronenberg F, Anker SD, Horwich TB, Fonarow GC. Epidemiology of dialysis patients and heart failure patients. Semin Nephrol. 2006; 26:118–133. [PubMed: 16530605]
2. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007; 71:31–38. [PubMed: 17091124]
3. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15:2208–2218. [PubMed: 15284307]
4. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006; 70:771–780. [PubMed: 16820797]
5. De Boer IH, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002; 13:2762–2769. [PubMed: 12397047]
6. Fellner SK, Lang RM, Neumann A, Bushinsky DA, Borow KM. Parathyroid hormone and myocardial performance in dialysis patients. Am J Kidney Dis. 1991; 18:320–325. [PubMed: 1882823]
7. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001; 12:2131–2138. [PubMed: 11562412]
8. Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. Kidney Int. 2002; 62:1724–1731. [PubMed: 12371973]
9. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000; 87:E10–E17. [PubMed: 11009570]
10. Kovesdy CP, Kalantar-Zadeh K. Vitamin D receptor activation and survival in chronic kidney disease. Kidney Int. 2008; 73:1355–1363. [PubMed: 18288097]
11. Guerin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000; 15:1014–1021. [PubMed: 10862640]
12. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003; 18:1731–1740. [PubMed: 12937218]
13. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000; 342:1478–1483. [PubMed: 10816185]
14. Kovesdy CP, Mehrotra R, Kalantar-Zadeh K. Battleground: chronic kidney disorders mineral and bone disease--calcium obsession, vitamin d, and binder confusion. Clin J Am Soc Nephrol. 2008; 3:168–173. [PubMed: 18045858]

15. Shinaberger CS, Greenland S, Kopple JD, Van WD, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? Am J Clin Nutr. 2008; 88:1511–1518. [PubMed: 19064510]
16. Collins AJ, Ma JZ, Ebben J. Impact of hematocrit on morbidity and mortality. Semin Nephrol. 2000; 20:345–349. [PubMed: 10928336]
17. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis. 1996; 28:53–61. [PubMed: 8712222]
18. Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. J Am Soc Nephrol. 2000; 11:335–342. [PubMed: 10665941]
19. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006; 17:1181–1191. [PubMed: 16565261]
20. Lefebvre P, Vekeman F, Sarokhan B, Enny C, Provenzano R, Cremieux PY. Relationship between hemoglobin level and quality of life in anemic patients with chronic kidney disease receiving epoetin alfa. Curr Med Res Opin. 2006; 22:1929–1937. [PubMed: 17022852]
21. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. Kidney Int. 2006; 69:560–564. [PubMed: 16395253]
22. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998; 339:584–590. [PubMed: 9718377]
23. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2005; 16:2180–2189. [PubMed: 15901766]
24. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355:2085–2098. [PubMed: 17108343]
25. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355:2071–2084. [PubMed: 17108342]
26. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet. 2007; 369:381–388. [PubMed: 17276778]
27. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol. 2005; 16:3070–3080. [PubMed: 16033854]
28. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. Nephrol Dial Transplant. 2004; 19:141–149. [PubMed: 14671049]
29. Streja E, Kovesdy CP, Greenland S, Kopple JD, McAllister CJ, Nissenson AR, Kalantar-Zadeh K. Erythropoietin, iron depletion, and relative thrombocytosis: a possible explanation for hemoglobin-survival paradox in hemodialysis. Am J Kidney Dis. 2008; 52:727–736. [PubMed: 18760517]
30. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008; 74:791–798. [PubMed: 18596733]
31. Fishbane S, Besarab A. Mechanism of increased mortality risk with erythropoietin treatment to higher hemoglobin targets. Clin J Am Soc Nephrol. 2007; 2:1274–1282. [PubMed: 17942772]

32. Kilpatrick RD, Critchlow CW, Fishbane S, Besarab A, Stehman-Breen C, Krishnan M, Bradbury BD. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. Clin J Am Soc Nephrol. 2008; 3:1077–1083. [PubMed: 18417744]
33. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990; 15:458–482. [PubMed: 2333868]
34. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, Shiohira Y, Fukiyama K. Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. Am J Kidney Dis. 1996; 28:541–548. [PubMed: 8840944]
35. Kovesdy CP, Regidor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Serum and dialysate potassium concentrations and survival in hemodialysis patients. Clin J Am Soc Nephrol. 2007; 2:999–1007. [PubMed: 17702709]
36. Beddhu S, Kaysen GA, Yan G, Sarnak M, Agodoa L, Ornt D, Cheung AK. Association of serum albumin and atherosclerosis in chronic hemodialysis patients. Am J Kidney Dis. 2002; 40:721–727. [PubMed: 12324906]
37. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. Kidney Int. 1993; 44:115–119. [PubMed: 8355451]
38. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H Jr, Kopple JD, Greenland S. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant. 2005; 20:1880–1888. [PubMed: 15956056]
39. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990; 15:458–482. [PubMed: 2333868]
40. Avram MM, Goldwasser P, Erroa M, Fein PA. Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of prealbumin and other nutritional and metabolic markers. Am J Kidney Dis. 1994; 23:91–98. [PubMed: 8285203]
41. Avram MM, Blaustein D, Fein PA, Goel N, Chattopadhyay J, Mittman N. Hemoglobin predicts long-term survival in dialysis patients: a 15-year single-center longitudinal study and a correlation trend between prealbumin and hemoglobin. Kidney Int Suppl. 2003:S6–11.
42. Chertow GM, Goldstein-Fuchs DJ, Lazarus JM, Kaysen GA. Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients. Kidney Int. 2005; 68:2794–2800. [PubMed: 16316355]
43. Goldwasser P, Michel MA, Collier J, Mittman N, Fein PA, Gusik SA, Avram MM. Prealbumin and lipoprotein(a) in hemodialysis: relationships with patient and vascular access survival. Am J Kidney Dis. 1993; 22:215–225. [PubMed: 8322786]
44. Mittman N, Avram MM, Oo KK, Chattopadhyay J. Serum prealbumin predicts survival in hemodialysis and peritoneal dialysis: 10 years of prospective observation. Am J Kidney Dis. 2001; 38:1358–1364. [PubMed: 11728975]
45. Sreedhara R, Avram MM, Blanco M, Batish R, Avram MM, Mittman N. Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. Am J Kidney Dis. 1996; 28:937–942. [PubMed: 8957050]
46. Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. Am J Clin Nutr. 2008; 88:1485–1494. [PubMed: 19064507]
47. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C. Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. Nephron. 1982; 31:103–110. [PubMed: 7121651]
48. Habib AN, Baird BC, Leypoldt JK, Cheung AK, Goldfarb-Rumyantzev AS. The association of lipid levels with mortality in patients on chronic peritoneal dialysis. Nephrol Dial Transplant. 2006; 21:2881–2892. [PubMed: 16735386]
49. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int. 2002; 61:1887–1893. [PubMed: 11967041]

50. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol. 2007; 18:293–303. [PubMed: 17167113]
51. Kalantar-Zadeh K, Kleiner M, Dunne E, Ahern K, Nelson M, Koslowe R, Luft FC. Total iron-binding capacity-estimated transferrin correlates with the nutritional subjective global assessment in hemodialysis patients. Am J Kidney Dis. 1998; 31:263–272. [PubMed: 9469497]
52. Ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim RM. Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: a prospective study. Kidney Int. 1999; 55:1945–1951. [PubMed: 10231458]
53. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990; 15:458–482. [PubMed: 2333868]
54. Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW. Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int. 2002; 62:2238–2245. [PubMed: 12427151]
55. Bommer J, Locatelli F, Satayathum S, Keen ML, Goodkin DA, Saito A, Akiba T, Port FK, Young EW. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004; 44:661–671. [PubMed: 15384017]
56. Wu DY, McAllister CJ, Kilpatrick RD, Dadres S, Shinaberger CS, Kopple JD, Kalantar-Zadeh K. Association between serum bicarbonate and death in hemodialysis patients: Is it better to be acidotic or alkalotic? Clin J Am Soc Nephrol. 2006; 1:70–78. [PubMed: 17699193]
57. Scholze A, Rattensperger D, Zidek W, Tepel M. Low serum leptin predicts mortality in patients with chronic kidney disease stage 5. Obesity (Silver Spring). 2007; 15:1617–1622. [PubMed: 17558000]
58. Axelsson J, Witasp A, Carrero JJ, Qureshi AR, Suliman ME, Heimburger O, Barany P, Lindholm B, Alvestrand A, Schalling M, Nordfors L, Stenvinkel P. Circulating levels of visfatin/pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. Am J Kidney Dis. 2007; 49:237–244. [PubMed: 17261426]
59. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol. 2002; 13:134–141. [PubMed: 11752030]
60. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P. Low triiodothyronine and survival in end-stage renal disease. Kidney Int. 2006; 70:523–528. [PubMed: 16775599]
61. Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? Semin Nephrol. 2009 Ref Type: In Press.
62. Chinen J, Shearer WT. Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol. 2008; 121:S388–S392. [PubMed: 18241688]
63. Hulsewe KW, van Acker BA, von Meyenfeldt MF, Soeters PB. Nutritional depletion and dietary manipulation: effects on the immune response. World J Surg. 1999; 23:536–544. [PubMed: 10227921]
64. Souba WW. Nutritional support. N Engl J Med. 1997; 336:41–48. [PubMed: 8970939]
65. Alexander JW. Immunoenhancement via enteral nutrition. Arch Surg. 1993; 128:1242–1245. [PubMed: 7694565]
66. Kimmel PL, Phillips TM, Lew SQ, Langman CB. Zinc modulates mononuclear cellular calcitriol metabolism in peritoneal dialysis patients. Kidney Int. 1996; 49:1407–1412. [PubMed: 8731107]
67. Erten Y, Kayatas M, Sezer S, Ozdemir FN, Ozyigit PF, Turan M, Haberal A, Guz G, Kaya S, Bilgin N. Zinc deficiency: prevalence and causes in hemodialysis patients and effect on cellular immune response. Transplant Proc. 1998; 30:850–851. [PubMed: 9595125]
68. Casciato DA, McAdam LP, Kopple JD, Bluestone R, Goldberg LS, Clements PJ, Knutson DW. Immunologic abnormalities in hemodialysis patients: improvement after pyridoxine therapy. Nephron. 1984; 38:9–16. [PubMed: 6472538]

69. Dobbelstein H, Korner WF, Mempel W, Grosse-Wilde H, Edel HH. Vitamin B6 deficiency in uremia and its implications for the depression of immune responses. Kidney Int. 1974; 5:233–239. [PubMed: 4362246]
70. DeSimone C, Famularo G, Tzantzoglou S, Trinchieri V, Moretti S, Sorice F. Carnitine depletion in peripheral blood mononuclear cells from patients with AIDS: effect of oral L-carnitine. AIDS. 1994; 8:655–660. [PubMed: 7914733]
71. Jandacek RJ, Anderson N, Liu M, Zheng S, Yang Q, Tso P. Effects of yo-yo diet, caloric restriction, and olestra on tissue distribution of hexachlorobenzene. Am J Physiol Gastrointest Liver Physiol. 2005; 288:G292–G299. [PubMed: 15513954]
72. Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, Coppack SW. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol. 1999; 277:E971–E975. [PubMed: 10600783]
73. Argiles JM. Cancer-associated malnutrition. Eur J Oncol Nurs. 2005; 9(Suppl 2):S39–S50. [PubMed: 16437757]
74. Lee PS, Waxman AB, Cotich KL, Chung SW, Perrella MA, Stossel TP. Plasma gelsolin is a marker and therapeutic agent in animal sepsis. Crit Care Med. 2007; 35:849–855. [PubMed: 17205019]
75. Rothenbach PA, Dahl B, Schwartz JJ, O'Keefe GE, Yamamoto M, Lee WM, Horton JW, Yin HL, Turnage RH. Recombinant plasma gelsolin infusion attenuates burn-induced pulmonary microvascular dysfunction. J Appl Physiol. 2004; 96:25–31. [PubMed: 12730154]
76. Christofidou-Solomidou M, Scherpereel A, Solomides CC, Christie JD, Stossel TP, Goelz S, DiNubile MJ. Recombinant plasma gelsolin diminishes the acute inflammatory response to hyperoxia in mice. J Investig Med. 2002; 50:54–60.
77. Ziegler TR, Evans ME, Fernandez-Estivariz C, Jones DP. Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. Annu Rev Nutr. 2003; 23:229–261. [PubMed: 12626687]
78. Pupim LB, Flakoll PJ, Ikizler TA. Nutritional supplementation acutely increases albumin fractional synthetic rate in chronic hemodialysis patients. J Am Soc Nephrol. 2004; 15:1920–1926. [PubMed: 15213282]
79. Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. J Am Soc Nephrol. 2006; 17:3149–3157. [PubMed: 17021267]
80. Stratton RJ, Bircher G, Fouque D, Stenvinkel P, de MR, Engfer M, Elia M. Multinutrient oral supplements and tube feeding in maintenance dialysis: a systematic review and meta-analysis. Am J Kidney Dis. 2005; 46:387–405. [PubMed: 16129200]
81. Czekalski S, Hozejowski R. Intradialytic amino acids supplementation in hemodialysis patients with malnutrition: results of a multicenter cohort study. J Ren Nutr. 2004; 14:82–88. [PubMed: 15060872]
82. Feldt-Rasmussen B, Lange M, Sulowicz W, Gafter U, Lai KN, Wiedemann J, Christiansen JS, El NM. Growth hormone treatment during hemodialysis in a randomized trial improves nutrition, quality of life, and cardiovascular risk. J Am Soc Nephrol. 2007; 18:2161–2171. [PubMed: 17554147]
83. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA. 1999; 281:1275–1281. [PubMed: 10208142]
84. Barton PA, Chretien C, Lau AH. The effects of nandrolone decanoate on nutritional parameters in hemodialysis patients. Clin Nephrol. 2002; 58:38–46. [PubMed: 12141405]
85. Navarro JF, Mora C, Macia M, Garcia J. Randomized prospective comparison between erythropoietin and androgens in CAPD patients. Kidney Int. 2002; 61:1537–1544. [PubMed: 11918762]
86. Galland R, Traeger J, Arkouche W, Cleaud C, Delawari E, Fouque D. Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. Kidney Int. 2001; 60:1555–1560. [PubMed: 11576372]
87. Galland R, Traeger J, Arkouche W, Delawari E, Fouque D. Short daily hemodialysis and nutritional status. Am J Kidney Dis. 2001; 37:S95–S98. [PubMed: 11158870]

88. Cano NJ, Fouque D, Roth H, Aparicio M, Azar R, Canaud B, Chauveau P, Combe C, Laville M, Leverve XM. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. J Am Soc Nephrol. 2007; 18:2583–2591. [PubMed: 17656473]

89. Bologa RM, Levine DM, Parker TS, Cheigh JS, Serur D, Stenzel KH, Rubin AL. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis. 1998; 32:107–114. [PubMed: 9669431]

90. Racki S, Zaputovic L, Mavric Z, Vujicic B, Dvornik S. C-reactive protein is a strong predictor of mortality in hemodialysis patients. Ren Fail. 2006; 28:427–433. [PubMed: 16825093]

91. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999; 55:648–658. [PubMed: 9987089]

92. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340:115–126. [PubMed: 9887164]

93. Kovesdy CP, Kalantar-Zadeh K. Novel targets and new potential: developments in the treatment of inflammation in chronic kidney disease. Expert Opin Investig Drugs. 2008; 17:451–467.

94. Handelman GJ, Walter MF, Adhikarla R, Gross J, Dallal GE, Levin NW, Blumberg JB. Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. Kidney Int. 2001; 59:1960–1966. [PubMed: 11318969]

95. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA, Himmelfarb J. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004; 65:1009–1016. [PubMed: 14871421]

96. Miyata T, Sugiyama S, Saito A, Kurokawa K. Reactive carbonyl compounds related uremic toxicity (“carbonyl stress”). Kidney Int Suppl. 2001; 78:S25–S31. [PubMed: 11168978]

97. Nguyen-Khoa T, Massy ZA, De Bandt JP, Kebede M, Salama L, Lambrey G, Witko-Sarsat V, Drueke TB, Lacour B, Thevenin M. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. Nephrol Dial Transplant. 2001; 16:335–340. [PubMed: 11158409]

98. Faggiotto A, Poli A, Catapano AL. Antioxidants and coronary artery disease. Curr Opin Lipidol. 1998; 9:541–549. [PubMed: 9868589]

99. Bayes B, Pastor MC, Bonal J, Junca J, Hernandez JM, Riutort N, Foraster A, Romero R. Homocysteine, C-reactive protein, lipid peroxidation and mortality in haemodialysis patients. Nephrol Dial Transplant. 2003; 18:106–112. [PubMed: 12480967]

100. Bayes B, Pastor MC, Bonal J, Foraster A, Romero R. Oxidative stress, inflammation and cardiovascular mortality in haemodialysis--role of seniority and intravenous ferrotherapy: analysis at 4 years of follow-up. Nephrol Dial Transplant. 2006; 21:984–990. [PubMed: 16326744]

101. Stenvinkel P, Diczfalusy U, Lindholm B, Heimburger O. Phospholipid plasmalogen, a surrogate marker of oxidative stress, is associated with increased cardiovascular mortality in patients on renal replacement therapy. Nephrol Dial Transplant. 2004; 19:972–976. [PubMed: 15031358]

102. Descamps-Latscha B, Witko-Sarsat V, Nguyen-Khoa T, Nguyen AT, Gausson V, Mothu N, London GM, Jungers P. Advanced oxidation protein products as risk factors for atherosclerotic cardiovascular events in nondiabetic predialysis patients. Am J Kidney Dis. 2005; 45:39–47. [PubMed: 15696442]

103. Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. Lancet. 2000; 356:1213–1218. [PubMed: 11072938]

104. Tepel M, van der GM, Statz M, Jankowski J, Zidek W. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. Circulation. 2003; 107:992–995. [PubMed: 12600912]

105. Wu MS, Yu CC, Yang CW, Wu CH, Haung JY, Hong JJ, Fan Chiang CY, Huang CC, Leu ML. Poor pre-dialysis glycaemic control is a predictor of mortality in type II diabetic patients on maintenance haemodialysis. Nephrol Dial Transplant. 1997; 12:2105–2110. [PubMed: 9351073]

106. Morioka T, Emoto M, Tabata T, Shoji T, Tahara H, Kishimoto H, Ishimura E, Nishizawa Y. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care. 2001; 24:909–913. [PubMed: 11347753]

107. McMurray SD, Johnson G, Davis S, McDougall K. Diabetes education and care management significantly improve patient outcomes in the dialysis unit. Am J Kidney Dis. 2002; 40:566–575. [PubMed: 12200809]

108. Oomichi T, Emoto M, Tabata T, Morioka T, Tsujimoto Y, Tahara H, Shoji T, Nishizawa Y. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. Diabetes Care. 2006; 29:1496–1500. [PubMed: 16801568]

109. Williams ME, Lacson E Jr, Teng M, Ofsthun N, Lazarus JM. Hemodialyzed type I and type II diabetic patients in the US: Characteristics, glycemic control, and survival. Kidney Int. 2006; 70:1503–1509. [PubMed: 16941022]

110. Tzamaloukas AH, Yuan ZY, Murata GH, Balaskas E, Avasthi PS, Oreopoulos DG. Clinical associations of glycemic control in diabetics on CAPD. Adv Perit Dial. 1993; 9:291–294. [PubMed: 8105946]

111. Tzamaloukas AH, Murata GH, Zager PG, Eisenberg B, Avasthi PS. The relationship between glycemic control and morbidity and mortality for diabetics on dialysis. ASAIO J. 1993; 39:880–885. [PubMed: 8123921]

112. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Association between glycemic control and mortality in diabetic patients with chronic kidney disease stage 1–5 not yet on dialysis. [Abstract]. J Am Soc Nephrol. 2007; 18:573A.

113. Kalantar-Zadeh K, Kopple JD, Regidor DL, Jing J, Shinaberger CS, Aronovitz J, McAllister CJ, Whellan D, Sharma K. A1C and survival in maintenance hemodialysis patients. Diabetes Care. 2007; 30:1049–1055. [PubMed: 17337501]

114. Kovesdy CP, Sharma K, Kalantar-Zadeh K. Glycemic Control in Diabetic CKD Patients: Where Do We Stand? Am J Kidney Dis. 2008

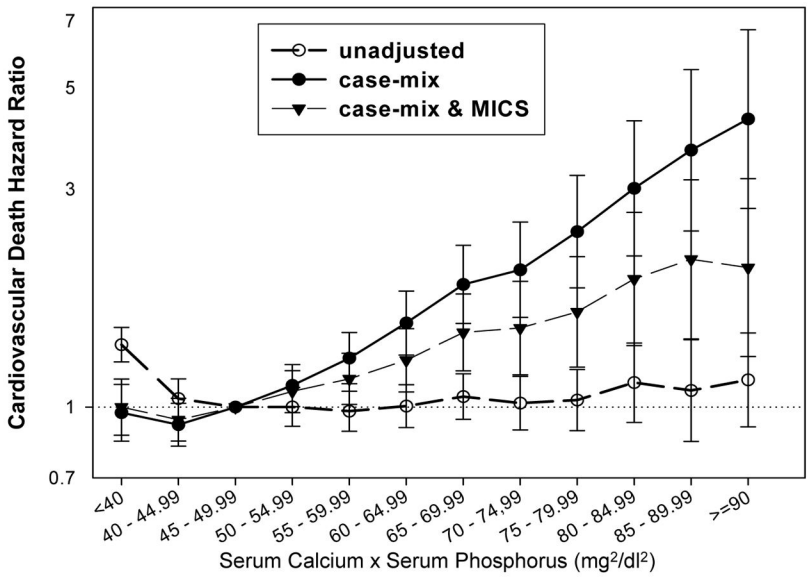

Figure 1.

Cardiovascular mortality associated with various levels of the calcium-phosphorus product in 58,058 maintenance hemodialysis patients. Based on data from Kalantar-Zadeh et al.[4]

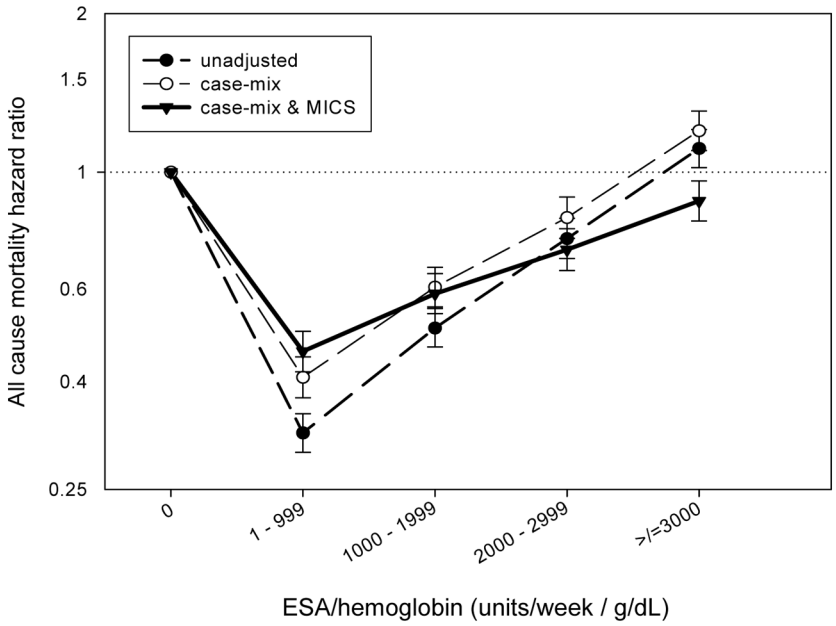

Figure 2.

All-cause mortality associated with the ratio of recombinant human erythropoetin dose and blood hemoglobin level in 58,058 maintenance hemodialysis patients. Based on data from Regidor et al.[19]

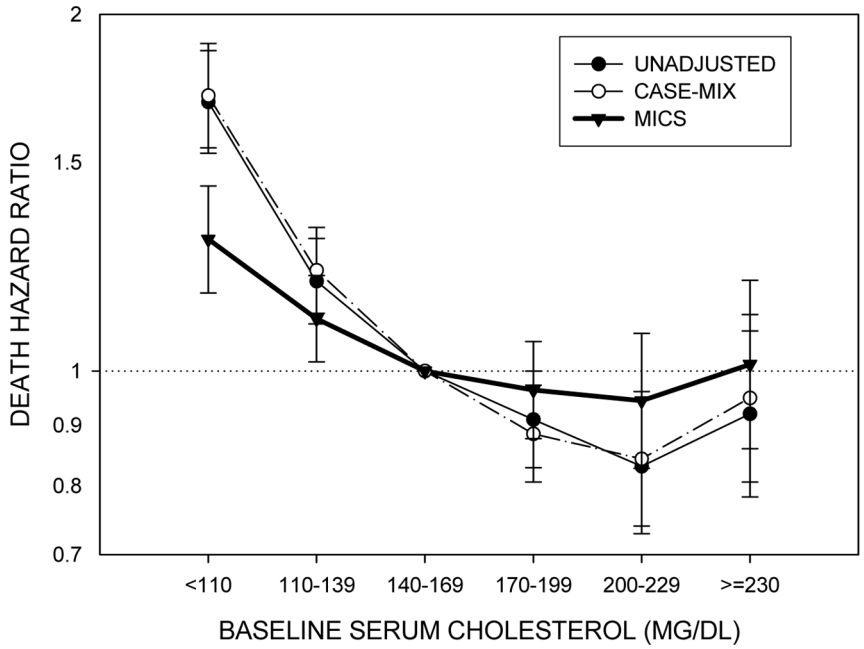

Figure 3.

All-cause mortality associated with various levels of baseline serum cholesterol in 15,859 patients receiving maintenance hemodialysis. Based on data from Kilpatrick et al.[50]

Table

Biomarkers	Putative mechanism of action of increased mortality	Therapeutic interventions
Nutritional markers: albumin, prealbumin, cholesterol, transferrin, creatinine, bicarbonate, leptin, visfatin, adiponectine, thyroid hormones, CRP, IL-6, TNF-α, serum amyloid A, lymphocyte count.	Complex, not well defined. May include effects mediated via lower muscle and fat mass, immune deficiency, insulin resistance and abnormal gastrointestinal function. Most biomarkers not causally involved in mechanism of action.	Oral or parenteral nutritional supplementation.[a,c] Anabolic therapies with human growth hormone or testosterone.[c] Daily dialysis.[c] Megestrol acetate.[c]
Markers of inflammation: CRP, IL-6, TNF-α, serum amyloid A, others.	Worsened atherosclerosis, endothelial dysfunction and oxidative stress.	Few studied explicitly for anti-inflammatory effect in CKD: Etanercept,[c] thiazolidinediones,[c] statins,[c] sevelamer hydrochloride.[c]
Markers of mineral and bone disorders: serum calcium, phosphorus, PTH, 25(OH) and $1,25(OH)_2$ vitamin D.	Vascular calcification. Various cardiovascular, metabolic, hematologic and immunologic abnormalities related to vitamin D metabolism and excess PTH.	Phosphate binders.[b] Treatment of secondary hyperparathyroidism with vitamin D-based therapies[c] and calcium sensing receptor sensitizers.[c]
Serum potassium.	Cardiac arrhythmias.	Renal replacement therapy in dialysis patients.[b] Medical interventions affecting renal and extra-renal potassium excretion and cellular distribution.[b]
Serum bicarbonate.	Muscle wasting, decreased albumin synthesis, impaired cardiac function and glucose homeostasis, accumulation of beta-2 microglobulin, chronic inflammation and disturbances in growth hormone and thyroid function.	Bicarbonate replacement through oral and/or parenteral supplementation.[c]
Markers of glycemic control: blood glucose, glycosylated hemoglobin and albumin, fructosamine,	Complex mechanism of action involving micro- and macro-vascular, neurological and immunological mechanisms.	Multiple hypoglycemic therapies.[3]

[a] Mortality benefit in randomized controlled trial in CKD.

[b] Mortality benefit implied based on mechanism of action.

[c] Benefit only proven on surrogate markers in CKD.

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