Title

Causes and consequences of the reverse epidemiology of body mass index in dialysis patients

Journal

Journal of Renal Nutrition, 15(1)

ISSN

1051-2276

Author

Kalantar-Zadeh, Kamyar

Publication Date

2005

DOI

10.1053/j.jrn.2004.09.020

Causes and Consequences of the Reverse Epidemiology of Body Mass Index in Dialysis Patients

Kamyar Kalantar-Zadeh, MD, PhD, MPH

A high body mass index (BMI) has been consistently shown to have a strong predictive correlation to decreased all-cause and cardiovascular mortality in maintenance hemodialysis (MHD) patients, ie, individuals with advanced chronic kidney disease undergoing maintenance dialysis. Indeed, according to some but not all, even morbid obesity (BMI $>$ 35 kg/m^2) confers survival advantages. Among the possible causes of reverse epidemiology of BMI are the following: (1) stable hemodynamic status in obesity, (2) higher concentrations of receptors of tumor necrosis factor-α and neurohormonal alterations in obesity, (3) time discrepancies among competitive risk factors, and (4) malnutrition–inflammation complex syndrome. The reverse epidemiology of BMI may have significant clinical and public health implications because interventions that can increase body weight and BMI in dialysis patients may improve survival in these individuals. However, this hypothesis should be tested in well-designed randomized trials. Until then, it is not reasonable to advocate obesity in MHD patients. On the other hand, categorically discrediting the theory of reverse epidemiology and calling it spurious without examining the true effect of weight-gaining interventions on the survival of dialysis patients is not scientifically or ethically appropriate.

EXTRAPOLATION OF THE PRINCIPLES of cardiovascular risk factors from the general population to dialysis patients may be wrong because dialysis populations may have a completely different epidemiology and risk factor constellation. Many observational studies have shown paradoxically inverse associations for the so-called conventional risk factors of cardiovascular disease and mortality in dialysis patients.[1] Indeed, a higher mortality in dialysis patients has been seen with a low, and not a high, body mass index (BMI).[2] This paradoxical association is more consistent in maintenance hemodialysis (MHD) patients as compared with chronic peritoneal dialysis patients. Similarly, blood pressure[3] and serum concentrations of cholesterol,[4] homocysteine,[5] and creatinine[6] also show a reverse epidemiology. A better understanding of the phenomenon of the reverse epidemiology of BMI in dialysis populations may not only help understand other risk factor reversals but also may lead to improved survival in MHD patients. This article reviews the reverse epidemiology of BMI in MHD patients and its possible causes and consequences as it pertains to the medical care of dialysis patients.

Division of Nephrology and Hypertension, Los Angeles Biomedical Institute at Harbor—UCLA Medical Center, Torrance, CA.

Presented at the 12th International Congress on Nutrition and Metabolism in Renal Disease, Venice and Padua, Italy, June 18 to 22, 2004.

Supported by the Young Investigator Award from the National Kidney Foundation and by a research grant from DaVita, Inc.

Address reprint requests to Kamyar Kalantar-Zadeh, MD, PhD, MPH, Department of Medicine and Pediatrics, Division of Nephrology and Hypertension, Harbor–UCLA Medical Center, Harbor Mailbox 406, 1000 West Carson St, Torrance, CA. Email: kamkal@ucla.edu

1051-2276/05/1501-0028$30.00/0
doi:10.1016/j.jrn.2004.09.020

BMI and Mortality in MHD Patients

A low BMI, for instance a BMI $<$ 25, is shown to be a strong predictor of high mortality risk in MHD patients.[7–12] Ironically, a BMI in the range of 20 to 25 is the recommended target for the general population.[13] Similarly, a high BMI, including an overweight state (BMI between 25

and 30) or obesity (BMI > 30), has been shown to paradoxically correlate with improved survival in MHD patients.[7-12] The inverse associations between BMI and mortality in MHD patients seem to be independent of serum albumin or other markers of nutritional status because most of the abovementioned studies are based on multivariate statistical adjustments including for serum albumin.

The Diaphane Study was one of the first studies that showed the reverse epidemiology of BMI in a cohort of 1,453 younger, mostly nondiabetic MHD patients followed up between 1972 and 1978.[14] Fleischmann et al[9] examined 1,346 predominately black MHD patients and found that the 1-year survival rate was significantly higher in the overweight patients. Leavy et al[8] showed that in a national sample of 3,607 MHD patients in the United States a low BMI was independently and significantly predictive of increased mortality. Wolf et al[15] studied the 2-year mortality risk in 9,165 MHD patients in the United States and showed that BMI was independently and inversely related to mortality when adjusted for age, diabetes, and Kt/V. Another similar study was conducted on 45,967 incident MHD patients.[16] Of the 3 body-size groups in this study, the lowest BMI group had a 42% higher mortality risk than the highest BMI tertile.[16] Kopple et al[17] found similar associations in 12,965 MHD patients, but instead of BMI, these investigators studied weight for height.

The Dialysis Outcomes and Practice Patterns Study[7] found the same reverse epidemiology of BMI in 9,714 MHD patients from the United States and Western Europe (1996 to 2000). Subanalysis based on overall health status resulted in similar inverse associations in all 3 comorbidity subgroups. Lowrie et al[18] recently studied mortality in 43,334 MHD patients according to body-size groups including the BMI. The mixed effects models suggested improved survival with increasing all of the body-size measures.[18] Glanton et al[12] also reported a reverse epidemiology of BMI in a historical cohort of 151,027 incident dialysis patients. Finally, Kalantar-Zadeh et al[19] recently examined the effect of both baseline BMI (classical Cox model) and changes in BMI over time (time-dependent model) on all-cause and cardiovascular mortality in a 2-year nonconcurrent cohort of approximately 58,000 MHD patients in the United States and showed that obesity, including morbid obesity (BMI > 35) was associated with survival advantages in virtually all subgroups of age, gender, race, dialysis vintage, serum albumin level, and Kt/V.[19]

Possible Explanations for Reverse Epidemiology

Hemodynamic State in Obese Individuals

Obese individuals usually have higher systemic blood pressure values.[20] Hence, their hemodynamic tolerance to afterload-reducing agents may be higher. Consequently, a larger proportion of obese patients tolerate such antihypertensive medications as angiotensin-converting enzyme inhibitors that are known to improve survival.[21]

Tumor Necrosis Factor-α Receptors and Neurohormonal Alterations

Cytokine and neuroendocrine profiles of obese patients may be altered.[20] Tumor necrosis factor-α (TNF-α) level is elevated in heart failure[22] and dialysis patients[23] and may contribute to poor survival through its proapoptotic and negative inotropic effects.[22] Adipose tissue produces soluble TNF- α receptors,[24] which may play a cardioprotective role because they neutralize the adverse biologic effects of TNF-α. Moreover, obesity has also been associated with alterations in the sympathetic nervous system and renin–angiotensin system because lean individuals have higher increases in plasma epinephrine and renin levels during treadmill testing despite similar baseline levels and history of hypertension.[25] Because heightened sympathetic and renin–angiotensin activity are associated with a poor prognosis in states of fluid overload,[26] diminished stress responses of the neurohormonal systems of obese MHD patients play a role in improving survival.

Time Discrepancies Between Competitive Risk Factors: Overnutrition Versus Undernutrition

Obesity and overnutrition are major risk factors for cardiovascular mortality in areas in which people have a greater life expectancy compared with individuals in other parts of the world.[27-33] In contrast, in developing countries, undernutrition is still a powerful determinant of morbidity and mortality, leading to a shorter life expectancy.[34-36] Similarly, survival advantages that ex-

ist in obese dialysis patients may, in the short term, outweigh the harmful effects of these risk factors on cardiovascular disease in the long term. Because MHD patients have a mortality risk that is much greater than that of the general population,[37,38] the long-term effects of these risk factors on future mortality may be overwhelmed by the short-term effects of other factors on dialysis mortality.

Malnutrition–Inflammation Complex Syndrome

Many studies have indicated that measures of protein-energy malnutrition (PEM) and inflammation are major predictors of clinical outcome in MHD patients.[39-47] MHD patients with cardiovascular disease have a higher prevalence of hypoalbuminemia, increased levels of inflammatory markers and cytokines, and a lower protein and energy intake than those without CVD.[43,46,48] Several factors, separately or working together, may engender PEM and/or inflammation in end-stage renal disease patients.[49] Many studies have shown a strong association between hypoalbuminemia and mortality in MHD patients.[50-53] A major mechanism for the development of PEM and its link to mortality in MHD patients may be proinflammatory cytokine activation associated with reduced kidney function and other proinflammatory comorbid conditions.[54] Increased release or activation of inflammatory cytokines, such as interleukin-6 or TNF-α, may suppress appetite, cause muscle proteolysis and hypoalbuminemia, and be involved in the processes that lead to atherosclerosis.[55] Because both PEM and inflammation are strongly associated with each other and can change many nutritional measures in the same direction, and because the relative contributions of measures of these 2 conditions to each other and to outcomes in MHD patients are not yet well defined, the term malnutrition–inflammation complex syndrome (MICS) has been suggested to denote the important contribution of both of these conditions to end-stage renal disease outcome.[49] The reverse epidemiology of obesity in MHD patients may mostly be attributable to MICS and its interplay with traditional cardiovascular risk factors.[1] Patients who are underweight may suffer from MICS.[49,56,57] MICS indicates a state of undernutrition, which may predispose to infection or other inflammatory processes.[54] Moreover, when individuals are malnourished and have a low BMI, they are more susceptible to inflammatory diseases.[49,54,58]

Should MHD Patients Gain Weight in Order to Live Longer?

To answer the above mentioned question, 2 more fundamental questions need to be answered first: (1) Is there an effective intervention that can lead to a significant gain in weight and possibly to improvement of nutritional markers in MHD patients? (2) If an effective intervention to gain weight can be found in MHD patients, will it prolong survival?

Currently, these 2 questions have remained unanswered. Indeed, virtually no major study has focused on weight gain as a primary outcome. This could be because obesity is generally considered unfavorable and a gain in weight undesirable, including in dialysis patients. However, with the emergence and further evolution of the field of reverse epidemiology, studies to that end are expected. Indeed a preliminary study recently showed that the appetite stimulator megestrol acetate, in lower-than-conventional doses (400 mg/day) for 16 weeks, led to an increase in weight and BMI in 10 MHD patients without any major adverse effect.[59] Moreover, megestrol acetate also increased serum albumin and decreased serum C-reactive protein levels.[59]

Undoubtedly, the absolute majority of observational studies, some of which were reviewed here, indicate that a higher BMI is associated with lower-than-expected mortality in MHD patients. However, it is possible that in the long run, overweight MHD patients, if they survive long enough, will suffer from more cardiovascular consequences. But do MHD patients survive that long? Recently Liu et al[60] showed that the reverse epidemiology of serum cholesterol was not present in those dialysis patients without evidence of MICS. However, the study sample was not representative of US dialysis patients, whose median age is 64.5 years,[61] whereas in the study by Liu et al it was 57.2 years for all patients and 53.7 years for those without MICS. Moreover, the investiators' own analyses in the subgroup of patients with MICS, who made up as much as 75% of all dialysis patients in the study, indicated either inverse or no association between total serum cholesterol and outcome even after adjust-

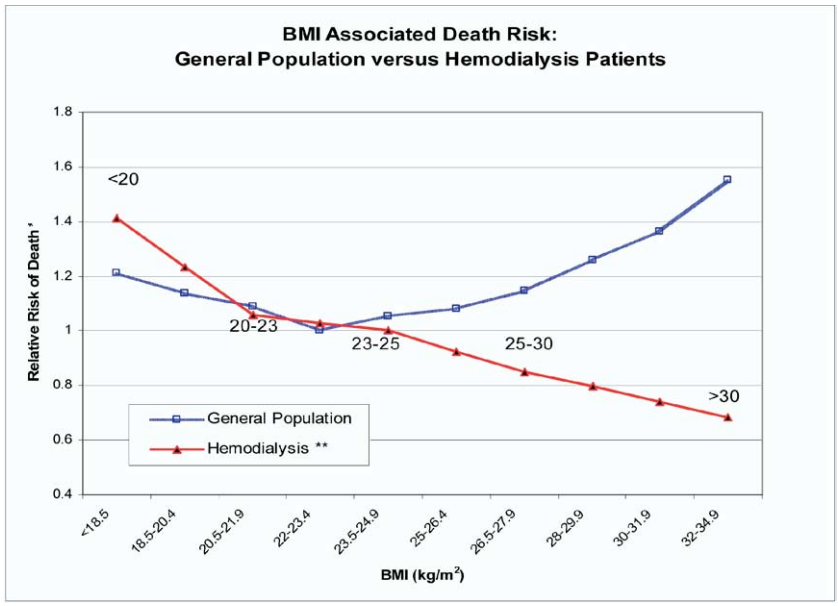

Figure 1. Reverse epidemiology of obesity in dialysis patients as compared with the general population.[1] Comparison between the impacts of body mass index (BMI) on all-cause mortality in the general population (■) versus in the maintenance hemodialysis population (▲). The general population data are from Calle et al (combined men and women, healthy, nonsmoking).[13] The hemodialysis data are from Leavey et al (combined US and European data).[6] *Note that each population has a different follow-up period: 14 years for the general population versus 4 years for hemodialysis patients. **BMI stratifications are different in 2 populations: X-axis data are based on the original graph of the general population, and the original hemodialysis BMI subgroup ranges are printed additionally along the hemodialysis curve. Adapted and reprinted with permission from Kidney International.[1]

ments for MICS.[62] These findings indicate a strong association between elements of MICS and prospective mortality in patients undergoing dialysis. Hence, the treatment of MICS may have a higher priority than treatment of hypercholesterolemia or other conventional cardiovascular risk factors in dialysis patients.[62]

Although the theory of reverse epidemiology (Fig 1) is largely based on observational studies, we caution against the use of the term spurious for the paradoxically inverse associations that have been consistently observed between such conventional risk factors as hypercholesterolemia and obesity and improved survival in MHD patients. Although the reverse epidemiology seems to be counterintuitive and against the contemporary principles of cardiovascular disease states, an unbiased approach is needed to examine the clinical and public health implications of it. It is quite possible that the dialysis population is one of several other similar subpopulations in whom a "bad-gone-good" phenomenon may indeed exist. Hence, better examination of the reverse epidemiology is needed and may lead to improved survival not only in MHD patients but also in such other similar groups as geriatric populations and patients with chronic heart failure.[63] Finally, it should be noted that as more effective treatments for MHD patents become available, it is possible that these patients will live longer, so that a reversal of the reverse epidemiology and a "back to traditional epidemiology" approach is observed, as is currently found in kidney transplantation patients.

References

1. Kalantar-Zadeh K, Block G, Humphreys MH, et al: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 63:793-808, 2003

2. Salahudeen AK: Obesity and survival on dialysis. Am J Kidney Dis 41:925-932, 2003

3. Zager PG, Nikolic J, Brown RH, et al: "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. Kidney Int 54:561-569, 1998

4. Nishizawa Y, Shoji T, Ishimura E, et al: Paradox of risk factors for cardiovascular mortality in uremia: Is a higher cholesterol level better for atherosclerosis in uremia? Am J Kidney Dis 38:S4-7, 2001

5. Kalantar-Zadeh K, Block G, Humphreys MH, et al: A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients. J Am Soc Nephrol 15:442-453, 2004

6. 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 15:458-482, 1990

7. Leavey SF, McCullough K, Hecking E, et al: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 16: 2386-2394, 2001

8. Leavey SF, Strawderman RL, Jones CA, et al: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 31:997-1006, 1998

9. Fleischmann E, Teal N, Dudley J, et al: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int 55:1560-1567, 1999

10. Wong JS, Port FK, Hulbert-Shearon TE, et al: Survival advantage in Asian American end-stage renal disease patients. Kidney Int 55:2515-2523, 1999

11. Abbott KC, Glanton CW, Trespalacios FC, et al: Body mass index, dialysis modality, and survival: Analysis of the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study. Kidney Int 65:597-605, 2004

12. Glanton CW, Hypolite IO, Hshieh PB, et al: Factors associated with improved short term survival in obese end stage renal disease patients. Ann Epidemiol 13:136-143, 2003

13. Calle EE, Thun MJ, Petrelli JM, et al: Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 341:1097-1105, 1999

14. Degoulet P, Legrain M, Reach I, et al: Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. Nephron 31:103-110, 1982

15. Wolfe RA, Ashby VB, Daugirdas JT, et al: Body size, dose of hemodialysis, and mortality. Am J Kidney Dis 35:80-88, 2000

16. Port FK, Ashby VB, Dhingra RK, et al: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 13:1061-1066, 2002

17. Kopple JD, Zhu X, Lew NL, et al: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int 56:1136-1148, 1999

18. Lowrie EG, Li Z, Ofsthun N, et al: Body size, dialysis dose and death risk relationships among hemodialysis patients. Kidney Int 62:1891-1897, 2002

19. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, et al: Time-dependant association between body mass index and cardiovascular mortality in hemodialysis patients. 37th annual conference of the American Society of Nephrology. J Am Soc Nephrol Nov 2004 (suppl)

20. Horwich TB, Fonarow GC, Hamilton MA, et al: The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 38:789-795, 2001

21. Fonarow GC, Chelimsky-Fallick C, Stevenson LW, et al: Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: The Hy-C trial. J Am Coll Cardiol 19:842-850, 1992

22. Feldman AM, Combes A, Wagner D, et al: The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 35:537-544, 2000

23. Kalantar-Zadeh K, Kopple JD, Humphreys MH, et al: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. Nephrol Dial Transplant 19:1507-1519, 2004

24. Mohamed-Ali V, Goodrick S, Bulmer K, et al: Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol 277:E971-975, 1999

25. Weber MA, Neutel JM, Smith DH: Contrasting clinical properties and exercise responses in obese and lean hypertensive patients. J Am Coll Cardiol 37:169-174, 2001

26. Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. N Engl J Med 341:577-585, 1999

27. Byers T: Body weight and mortality. N Engl J Med 333:723-724, 1995

28. Manson JE, Willett WC, Stampfer MJ, et al: Body weight and mortality among women. N Engl J Med 333:677-685, 1995

29. Lew EA, Garfinkel L: Variations in mortality by weight among 750,000 men and women. J Chronic Dis 32:563-576, 1979

30. Macdonald FC: Quetelet index as indicator of obesity. Lancet 1:1043, 1986

31. Kushner RF: Body weight and mortality. Nutr Rev 51:127-136, 1993

32. Klag MJ, Ford DE, Mead LA, et al: Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med 328:313-318, 1993

33. Cui Y, Blumenthal RS, Flaws JA, et al: Non–high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 161:1413-1419, 2001

34. Combating undernutrition in the Third World. Lancet 1:334-336, 1988

35. Collins S, Myatt M: Short-term prognosis in severe adult and adolescent malnutrition during famine: Use of a simple prognostic model based on counting clinical signs. JAMA 284: 621-626, 2000

36. Salama P, Assefa F, Talley L, et al: Malnutrition, measles, mortality, and the humanitarian response during a famine in Ethiopia. JAMA 286:563-571, 2001

37. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 9:S16-23, 1998

38. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32:S112-119, 1998

39. Kalantar-Zadeh K, Kopple J: Malnutrition as a cause of morbidity and mortality in dialysis patients, in Kopple J, Massry S (eds): Nutritional Management of Renal Disease (ed 2). Philadelphia, Lippincott Williams & Wilkins, 2004

40. Chung SH, Lindholm B, Lee HB: Is malnutrition an independent predictor of mortality in peritoneal dialysis patients? Nephrol Dial Transplant 18:2134-2140, 2003

41. Stenvinkel P, Barany P, Heimburger O, et al: Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? Kidney Int Suppl 2:103-108, 2002

42. Kalantar-Zadeh K, Kopple JD, Block G, et al: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 38:1251-1263, 2001

43. Bergstrom J: Inflammation, malnutrition, cardiovascular disease and mortality in end- stage renal disease. Pol Arch Med Wewn 104:641-643, 2000

44. Koretz RL: Does nutritional intervention in protein-energy malnutrition improve morbidity or mortality? J Ren Nutr 9:119-121, 1999

45. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality. Perit Dial Int 19:S309-314, 1999

46. Ritz E, Vallance P, Nowicki M: The effect of malnutrition on cardiovascular mortality in dialysis patients: Is L-arginine the answer? Nephrol Dial Transplant 9:129-130, 1994

47. Acchiardo SR, Moore LW, Latour PA: Malnutrition as the main factor in morbidity and mortality of hemodialysis patients. Kidney Int Suppl 16:S199-203, 1983

48. Fung F, Sherrard DJ, Gillen DL, et al: Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients. Am J Kidney Dis 40:307-314, 2002

49. Kalantar-Zadeh K, Ikizler TA, Block G, et al: Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis 42:864-881, 2003

50. Foley RN, Parfrey PS, Harnett JD, et al: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol 7:728-736, 1996

51. Kaysen GA, Rathore V, Shearer GC, et al: Mechanisms of hypoalbuminemia in hemodialysis patients. Kidney Int 48:510-516, 1995

52. Danielski M, Ikizler TA, McMonagle E, et al: Linkage of hypoalbuminemia, inflammation, and oxidative stress in patients receiving maintenance hemodialysis therapy. Am J Kidney Dis 42:286-294, 2003

53. Kalantar-Zadeh K, Kilpatrick RD, Kuwae K, et al: Population attributable mortality risk for albumin <3.8 g/dL: How many lives can be saved if hypoalbuminemia can be corrected in hemodialysis patients? 37th annual conference of the American Society of Nephrology. J Am Soc Nephrol Nov 2004 (suppl)

54. Kalantar-Zadeh K, Kopple J: Inflammation in renal failure, in Rose B (ed): UpToDate (since Oct 2002). Wellesley, MA, UpToDate, Inc, 2004

55. Kalantar-Zadeh K, Block G, McAllister CJ, et al: Appetite and inflammation, nutrition, anemia and clinical outcome in hemodialysis patients. Am J Clin Nutr 80:299-307, 2004

56. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality: An integrated point of view. Am J Kidney Dis 32:834-841, 1998

57. Ritz E: Why are lipids not predictive of cardiovascular death in the dialysis patient? Miner Electrolyte Metab 22:9-12, 1996

58. Kalantar-Zadeh K, Kopple JD: Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis 38:1343-1350, 2001

59. Rammohan M, Kalantar-Zadeh K, Liang A, et al: Megestrol acetate in moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. J Ren Nutr 2005, in press

60. Liu Y, Coresh J, Eustace JA, et al: Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. JAMA 291:451-459, 2004

61. System USRD: USRD 2003 Annual Data Report; Atlas of End Stage Renal Diseases in the United States. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2003

62. Kalantar-Zadeh K, Anker SD: Inflammation, cholesterol levels, and risk of mortality among patients receiving dialysis. JAMA 291:1834, 1834-1835, 2004

63. Kalantar-Zadeh K, Block G, Horwich T, et al: Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 43:1439-1444, 2004