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Scholarly Review

The kidney disease wasting: Inflammation, oxidative stress, and diet-gene interaction

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Abstract

The 350,000 maintenance hemodialysis (MHD) patients in the United States have an unacceptably high mortality rate of >20%/year. Almost half of all deaths are assumed to be cardiovascular. Markers of kidney disease wasting (KDW) such as hypoalbuminemia, anorexia, body weight and fat loss, rather than traditional cardiovascular risk factors, appear to be the strongest predictors of early death in these patients. The KDW is closely related to oxidative stress (SOX). Such SOX markers as serum myeloperoxidase are associated with pro-inflammatory cytokines and poor survival in MHD patients. Identifying the conditions that modulate the KDW/SOX-axis may be the key to improving outcomes in MHD patients. Dysfunctional lipoproteins such as a higher ratio of the high-density lipoprotein inflammatory index (HII) may engender or aggravate the KDW, whereas functionally intact or larger lipoprotein pools, as in hypercholesterolemia and obesity, may mitigate the KDW in MHD patients. Hence, a reverse epidemiology or “bad-gone-good” phenomenon may be observed. Diet and gene and their complex interaction may lead to higher proportions of pro-inflammatory or oxidative lipoproteins such as HII, resulting in the aggravation of the SOX and inflammatory processes, endothelial dysfunction, and subsequent atherosclerotic cardiovascular disease and death in MHD patients. Understanding the factors that modulate the KDW/SOX complex and their associations with genetic polymorphism, nutrition, and outcomes in MHD patients may lead to developing more effective strategies to improve outcomes in this and the 20 to 30 million Americans with chronic disease states such as individuals with chronic heart failure, advanced age, malignancies, AIDS, or cachexia.

Key words: Kidney disease wasting, inflammation, malnutrition, reverse epidemiology, oxidative stress, genetic polymorphism

POOR OUTCOME IN DIALYSIS PATIENTS

In the United States, there are currently ~350,000 individuals with chronic kidney disease (CKD) stage 5 (CKD-5)

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who undergo maintenance hemodialysis (MHD) treatment (92%) or chronic peritoneal dialysis treatment (8%) to survive.¹ The number of dialysis outpatients will surpass one-half million by 2010 and 1 million by 2017.² Yet, the CKD-5 patient population is only the tip of the iceberg of all individuals with CKD, who are estimated to be 20 million Americans.³

The MHD patients experience lower quality of life, higher hospitalization rates, and increased death, currently >20%/year in the United States, despite many recent improvements in dialysis treatment and techniques.¹ Ap-

proximately 2/3 of all MHD patients die within 5 years of the initiation of dialysis treatment, a 5-year survival worse than most cancers.⁴ Almost half of all MHD patients die presumably of cardiovascular diseases.^{1,2,4} Extrapolation of findings from the general population has led to decades of focusing on treating such *conventional* cardiovascular risk factors in dialysis patients as hypertension, hypercholesterolemia, obesity, and hyperhomocysteinemia. However, survival has not improved substantially in the past 2 decades.^{1,2,4} Similarly, in the recently conducted *Die Deutsche Diabetes Dialysis* (4D) Study,⁵ survival did not improve in diabetic dialysis patients who received atorvastatin for up to 4 years. Clinical trials using folic acid to correct hyperhomocysteinemia in dialysis patients are reported to be negative.^{6–8} Additional efforts targeting dialysis dose or membrane including in the HEMO⁹ and ADEMEX¹⁰ studies failed to show any significant survival impact.¹⁰ Hence, other prevailing risk factors must contribute to this substantial and persistent mortality risk. Nutrition appears to be on top of the list.

RISK FACTOR PARADOXES IN MHD PATIENTS

In industrialized and affluent nations, *under*-nutrition, usually referred to as malnutrition, is an uncommon cause of poor outcome in the general population, where instead “*over*-nutrition” is associated with a greater risk of cardiovascular disease and shortened survival. In contrast, in MHD patients, an “obesity paradox” exists, in that obesity is associated with better survival.^{11,12} A large epidemiologic study recently examined the mortality predictability of both the absolute magnitude of the weight-for-height surrogates such as body mass index (BMI) and changes in weight over time in a 2-year cohort of 54,535 MHD patients of the second largest dialysis care provider in the United States (DaVita Inc., El Segundo, CA, U.S.A.).¹³ The study showed that obesity, including morbid obesity (BMI > 35 kg/m²), was associated with survival advantages in virtually all subgroups of age, gender, race, dialysis vintage, serum albumin, and Kt/V.¹³ Moreover, for the first time, weight loss was found to be associated with increased mortality, whereas weight gain conferred survival advantages¹³ (Figure 1). In another recent study, total body fat was directly measured in 535 MHD patients both at baseline and after 6 months, and patients were followed for up to 3.5 years.¹⁴ The investigators found that not only was lower total body fat associated with higher mortality (Figure 2), but loss of body fat over time was associated with increased death risk compared with fat gain.¹⁴

Figure 1 Relative risk of death for changes in weight over time in 54,535 maintenance hemodialysis patients who were followed from July 2001 to June 2003, adjusted for case-mix and laboratory values (Adapted with permission from Kalantar-Zadeh et al.: Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis* 2005; 46:489–500).

The foregoing findings may suggest that a larger body fat mass as seen in obesity probably represents protective reserves that may mitigate the adverse effects of malnutrition in MHD patients. This counterintuitive “reverse epidemiology” of cardiovascular risks is not only observed for obesity but also for other indicators of over-nutrition and metabolic syndrome including

Figure 2 Hazard ratios of 30-month death across the body fat categories in 535 maintenance hemodialysis patients (Adapted with permission from Kalantar-Zadeh et al.: Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr* 2006;83:202–210).

hypertension and hypercholesterolemia, both of which are paradoxically associated with better survival in these patients.^{15,16} Indeed, in addition to the MHD population, over 20 million Americans including those with chronic heart failure (CHF), AIDS, rheumatoid arthritis, or malignancy, and possibly elderly individuals exhibit similar risk factor paradoxes.^{4,17} Hence, the key to improving survival in MHD patients and other similar populations may be better understanding the mechanisms that lead to these paradoxical alterations.¹⁶

KIDNEY DISEASE WASTING (KDW)

Maintenance hemodialysis patients have a high prevalence of protein-energy malnutrition (20–60%) and inflammation (15–50%),^{18–23} both of which are strongly associated with many nutritional measures, such as appetite and serum albumin, and clinical outcomes in the *same direction*. As yet, the relative contributions of measures of these 2 conditions to each other and to outcomes are not well defined; therefore, we and others have suggested the term “malnutrition-inflammation complex (or cachexia) syndrome” (MICS) to denote the important contribution of these conditions to poor outcome.^{18,24} Other terms have also been suggested including the “Malnutrition-Inflammation-Atherosclerosis” (MIA) syndrome²⁵ to underscore the MICS association with cardiovascular disease, and the “KDW,” a recently proposed term during a consensus conference.²⁶ In this review article, we use the term KDW to indicate the MICS or MIA interchangeably.

The etiology of the KDW in MHD patients is not clear, but a major role-player may be decreased appetite, or anorexia, which per se may be a consequence of inflammation in MHD patients.²⁷ In a recent study in 331 MHD patients, anorectic individuals had higher serum levels of pro-inflammatory cytokines and increased death risk and hospitalization rate.²⁷ A recent large epidemiologic study in 58,058 MHD patients showed that a decline in serum albumin over 6 months was associated with increased death risk in the upcoming 18 months, whereas an increase in serum albumin during the same period conferred improved survival.²⁸ Another recent study has shown that an increase in protein intake, up to 1.4 g/day/kg body weight, was associated with the greatest survival in MHD patients.²⁹

The foregoing findings on the strong and consistent associations between the surrogates of the KDW and survival in MHD patients have led us to advance several hypotheses pertaining to the core status of the KDW in the survival of MHD patients. The KDW probably results

from the complex interactions between diet, gene, and other prevailing conditions including uremia and dialysis treatment modalities, and is associated with inflammation, anorexia, malnutrition, and oxidative stress (SOX). Hence, the KDW can lead to wasting, atherosclerosis, poor cardiovascular outcome, and what appears to be the reverse epidemiology, as we have schematically depicted in Figure 3. The remaining of this review article focuses on the potential pathophysiologic pathways of the KDW and its core components in MHD patients.

CARDIOVASCULAR RISKS AND THE TEMPORAL DISCORDANCE HYPOTHESIS

In the general population, inflammatory markers such as serum C-reactive protein (CRP) are stronger predictors of cardiovascular events than LDL hypercholesterolemia.^{30,31} Because inflammation, a main component of the KDW, is much more common in MHD patients,^{32,33} it may be argued that the KDW is the main cause of the cardiovascular epidemic through its inflammatory arm.³⁴ Indeed, the 2 main KDW surrogates, i.e., hypoalbuminemia and anorexia, are both associated with inflammation and strong predictors of cardiovascular death in MHD patients,^{27,28,35} whereas traditional cardiovascular risk factors are not. Hence, at least by virtue of its inflammatory component, KDW might cause direct endothelial dysfunction via stimulation of intercellular adhesion molecules.³⁶

It is important to note that in the general population, inflammation, similar to the traditional cardiovascular risk factors, exerts its deleterious effects on a “long-term” basis; hence, many years to decades are required before clinically overt cardiovascular disease can emerge. However, in MHD patients, the KDW appears to result in poor outcome within a much “shorter” period of time. This *temporal discordance*, probably another important key element in the pathophysiology of the KDW,^{4,32,37} may be one of the most distinguishing features of the risk-outcome interplay in MHD patients. In epidemiologic studies, this phenomenon can be referred to as “time-discrepancy between the competing risk factors,”¹⁵ i.e., over-nutrition, which is the long-term killer, vs. under-nutrition, which is the short-term killer. In other words, MHD patients do not live long enough to die of over-nutrition, because they die much faster of under-nutrition. The mentioned time discordance may also be related to the *rapid* contraction of the protective lipoprotein pool and simultaneous development of highly pro-inflammatory and oxidative lipoprotein properties. Genetic

Figure 3 Schematic representation of the pathophysiology of the Kidney Disease Wasting in maintenance hemodialysis patients.

polymorphism and diet may modulate both the lipoprotein contraction and the alteration of the lipoprotein properties, i.e., the conversion of anti-inflammatory to pro-inflammatory properties.^{38,39}

SOX IN MHD PATIENTS

Oxidative stress implies the potential of tissue damage from an imbalance between excessive generation of oxidant compounds and insufficient antioxidant defense mechanisms.^{40,41} The generation of oxidative compounds represents part of the defense mechanisms against invading microorganisms and malignant cells as well as of tissue healing and remodeling. It is an important step in inflammation and tissue repair processes.⁴¹ However, an improper or maladaptive activation of oxidative processes

may be chronically present in pathological situations, such as uremia, contributing to chronic cell and tissue injury.^{42,43}

In MHD patients, the balance between pro-oxidant and anti-oxidant capacity appears shifted toward an increased SOX.⁴² Blood levels of several lipid and protein oxidation products such as F2 isoprostanes are increased in MHD patients.^{44,45} Neutrophils of MHD patients overproduce reactive oxygen species (ROS) in response to activating stimuli.^{46,47} Reduced intake of vitamin C and some other anti-oxidant vitamins and carotenoid compounds has been reported in MHD patients.⁴⁸ These pro-oxidative constellation can be a result of imposed dietary restriction of fresh fruits and vegetables to avoid hyperkalemia and to restrict phosphorus and calcium intake in MHD patients. Hence, it is possible that nephrologists and dieti-

tians adamantly force MHD patients into intake of an atherogenic diet.⁴⁸

Other possible mechanisms of SOX in MHD patients include loss of antioxidant vitamins during HD, reduced intracellular levels of vitamin E, reduced selenium pool, and deficiency in the glutathione scavenging system.^{49–51} At the same time, pro-oxidant activity is increased in MHD patients due to advanced age, higher prevalence of diabetes and other comorbid conditions, inflammation per se, HD treatment, and freely circulating endotoxins, especially in the setting of hypocholesterolemia.^{41,46,51–53} Hence, in the setting of such a highly pro-oxidant milieu, the role of anti-inflammatory and anti-oxidant lipoproteins may be extremely crucial.

OXIDATIVE, INFLAMMATORY, AND CARBAMYLATED LIPOPROTEINS

Lipoprotein oxidation^{54–58} and/or carbamylation^{59,60} may aggravate atherogenic processes. Exposure to urea may lead to the carbamylated proteins, which are shown to destroy endothelial cells by apoptosis.⁵⁹ In MHD patients, total plasma protein carbamylation is several times higher than in controls,⁵⁹ which may be a cause of cardiovascular epidemic in these patients. Oxidized phospholipids may be generated abundantly by potent oxidants via lipooxygenase and myeloperoxidase (MPO) pathways.^{54,61,62} In a recent study, serum MPO was found to be associated with markers of inflammation and prospective mortality in MHD patients.⁶³

The processes related to SOX may lead to *pro-inflammatory conversion* of even such protective lipoproteins as high-density lipoprotein (HDL). Hence, the assessment of *HDL inflammatory index* (HII)^{54,58,64} may provide insights into the accelerated and paradoxical atherogenesis process in MHD patients with hypocholesterolemia, in whom lipoproteins may be pro-inflammatory and pro-oxidants. The HII has recently been shown to distinguish patients at high risk from cardiovascular disease from control subjects better than the absolute HDL levels.⁶⁵ To our knowledge, with the exception of our limited preliminary data,^{38,39} no other studies are available. High-density lipoprotein inflammatory index or other specific pro/anti-inflammatory and pro/anti-oxidative *properties* (not *structure*) of lipoproteins have not yet been studied in CKD patients, nor has their role been examined in the development of the KDW and poor clinical outcome.

In some individuals with coronary atherosclerosis, high levels of pro-inflammatory LDL have been found despite normal to low blood lipid levels or normal to high plasma HDL levels.⁵⁸ Maintenance hemodialysis patients may

belong to these apparently hypocholesterolemic populations.⁶⁶ Paraoxonase, one of the enzymes shown to prevent the formation of oxidized LDL, has been shown to be low in MHD patients,^{67,68} but its role in the context of the KDW is unknown. Examining inflammatory and oxidative properties of lipoproteins and their modulation by diet or gene polymorphisms may be the key to understanding the unique susceptibility of MHD and other CKD patients to atherosclerosis. However, these associations need to be investigated in the context of complex and *integrated* models as we have delineated in Figure 3.

THE ENDOTOXIN-LIPOPROTEIN HYPOTHESIS

A low serum cholesterol is not only a predictor of poor outcome in MHD patients but also in individuals with CHF,⁶⁹ malignancy, AIDS, and cachexia,^{15,70–72} where inflammation and SOX are dominating conditions.^{73–75} Serum cholesterol is a surrogate of the *totality of lipoproteins*. Freely circulating lipopolysaccharides (LPS) activate the pro-inflammatory cytokine cascade, leading to the KDW/SOX complex.^{76–78} Hence, intact (not oxidized) lipoproteins may be a *defense mechanism* against inflammation by binding to and neutralizing the circulating LPS.^{79,80} Higher levels of endotoxins have been observed in both MHD and CHF patients.^{76,77,81} In malnourished or inflamed MHD patients with a low cholesterol level or *dysfunctional* lipoproteins, the LPS bioactivity can practically increase even without more absolute LPS on board, leading to pro-inflammatory cytokine activation cascade,^{15,69,82} especially in the setting of pro-atherogenic diet and pro-inflammatory genetic polymorphism.

DIET AND POOR OUTCOME IN MHD PATIENTS

We and others have consistently demonstrated that low serum albumin level^{28,83} and decreased protein intake (low protein nitrogen appearance or nPNA or nPCR)^{29,84} are strongly associated with mortality in MHD patients. Although deficiency of *macronutrients* (protein and energy) alone may accentuate inflammation and SOX as shown in animal models,⁸⁵ *micronutrients* may be as important. Hence, nutrients may exert a *combined* (rather than individual) impact on modulating inflammation and SOX in MHD patients.^{32,37}

Two recent studies using unconventional vegetarian⁸⁶ or Mediterranean-style⁸⁷ diets showed that diet can mitigate inflammation and associated cardiovascular risk in non-CKD populations. Foods may contain *neutraceuticals*

that can modulate the synthesis or activity of inflammatory or oxidative mediators or gene expression.^{88–90} Another example is the anti-inflammatory and anti-oxidative effects of dietary fish oil shown in several studies.^{90–95} Kutner et al.⁹⁵ found that dialysis patients consuming more fish were less likely to die. Fish oil is an abundant source of eicosapentaenoic acid (EPA), a precursor of certain prostaglandins and leukotrienes with anti-inflammatory properties.^{96–98} A recent pilot clinical trial showed that hypoalbuminemia improved in MHD patients who were offered nutritional supplements with such anti-inflammatory and anti-oxidant ingredients as fish oil, borage oil, vitamin E, and carnitine.⁹⁹

Appetite-stimulating agents may play a beneficial role in improving nutritional intake and outcome in MHD patients.¹⁰⁰ However, data on use of appetite-stimulating agents in CKD patients are exceptionally scarce.^{32,37} Finally, the ongoing challenge that has remained to be resolved is to develop practical tools for the accurate measurement of dietary intake in CKD patients. During the first few years of the “Nutritional and Inflammation Evaluation in Dialysis” (NIED) Study,¹⁰¹ we have developed unique techniques including CKD-specific food frequency questionnaires⁴⁸ and dietary interviews to assess their distinct dietary intake. The developed food frequency instruments are currently used in several longitudinal studies on MHD patients.¹⁰¹

GENE POLYMORPHISM AND THE KDW/SOX AXIS

Genetic factors may play a major role in the KDW/SOX axis, because the incidence and prevalence of the KDW and SOX are highly variable among MHD patients and because such variations cannot solely be explained by diet, dialysis technique, or clinical factors. Most (up to 90% or more) CKD patients die before they reach the CKD-5 stage.¹⁰² Thus, we hypothesize that a significant “survival selection process” may lead to the elimination of most individuals with earlier CKD stages,¹⁰² resulting in the existence of only a small but highly selected group of surviving individuals with a higher prevalence of certain genotypes that are associated with KDW/SOX susceptibility. In other words, those few CKD patients who appear “lucky” to survive long enough to reach the CKD-5 stage and undergo dialysis treatment may eventually be the “unlucky” ones if they are susceptible to SOX and KDW in the setting of CKD-5 stage and dialysis treatment. A recent animal study showed that CRP directly inhibits the binding of leptin to its receptors and blunts completely the actions of leptin such as decreased appetite and

hypercatabolism.¹⁰³ Because CRP has been correlated with increased adiposity and plasma leptin in the general population, we hypothesize that genetic constellations that are associated with high circulating CRP and leptin resistance may lead to overnutrition and obesity, which are risk factors for reaching CKD-5.^{104,105} This hypothesis may also explain why the traditional cardiovascular risk factors are less relevant or even paradoxical in MHD patients, whereas such nontraditional factors as the KDW/SOX complex emerge as the strongest survival predictors.^{4,15}

A substantial heritability (35–40%) for CRP and albumin levels and leukocytes have been reported in non-CKD populations with heart disease.¹⁰⁶ Similarly, individual factors may significantly influence the levels of inflammatory markers in dialysis patients.¹⁰⁷ Because dialysis patients of Asian origin have lower CRP levels and better survival,¹⁰⁸ it could be argued that either the Asian diet or genetic factors or both may account for the observed differences. Indeed, Szalai et al.,¹⁰⁹ reported that the prevalence of a polymorphic GT repeat in the intron of the CRP gene, which contributes to variations in baseline CRP, was 2-fold higher in Caucasians than in African Americans. Thus, single-nucleotide polymorphisms (SNPs) in cytokine genes may have a significant influence on inflammation and its attendant morbidity in MHD patients.

Although genetic factors such as SNPs may have a modest effect at an individual level, because of their presumably high frequency in the MHD population (see “survival selection” hypothesis above), these genetic variants can be associated with a high attributable risk of cardiovascular disease and death. It should be noted that polymorphisms do not exist in isolation. The combination of base changes at several sites (haplotypes) may indeed influence function. Hence, haplotype methods may capture most of the genetic variation across sizable regions using a small number of haplotype tag SNPs.^{110,111}

SNPS IN CANDIDATE CYTOKINE GENES

Within candidate genes, the number of common polymorphisms is finite,¹¹² but a direct assay of all existing common polymorphism is inefficient, because genotypes at many of these sites are strongly correlated. Thus, it is not necessary to assay all common variants if the patterns of allelic association between common variants can be described. Selection of the maximally informative set of a common tag SNP set can comprehensively interrogate for main effects from common functional variation.^{113,114} In studies pertaining to the interaction between diet and

gene in MHD patients, the SNPs should be chosen not only based on the regulatory effect on gene transcription but also on the evidence supporting their clinical significance.

PITFALLS OF GENETIC STUDIES IN MHD PATIENTS

One of the sometimes overlooked aspects of cytokine-disease association studies is that the cytokine network is highly complex, containing interactive cascades of gene activation and suppression. Therefore, individual genetic polymorphisms in cytokine gene association may be non-informative, whereas specific *combinations* of cytokine genotypes might predispose to disease susceptibility or outcome. Environmental factors including *diet* may modify the molecular function of the gene product under observation. The importance of gene-diet interaction is that only when an individual with a high genetic risk profile enters into a high-risk environment, such as the atherogenic diet imposed upon MHD patients, will the effect be so great that premature cardiovascular disease develops. This is exemplified by the observation by Humphries et al.,¹¹⁵ that the greatest risk for cardiovascular disease is in males who smoke and carry the -174 C allele (IL-6). Early interventions can be most effective in the high-risk genotypes subjects, who develop ESRD and have a higher portion of inflammatory lipoproteins while subjected to dietary restriction with low potassium and phosphorus intake.⁴

CONCLUSIONS AND FUTURE STEPS

The KDW, rather than traditional cardiovascular risk factors, appears to be among the strongest predictors of early death in MHD patients. Anorexia and a hypercatabolic state are common features of the KDW and are both related to poor survival. The KDW appears to be closely associated with the SOX. Dysfunctional lipoproteins with pro-inflammatory and oxidative properties such as HII may lead to KDW, whereas functionally intact lipoproteins or a larger lipoprotein pool may protect against the KDW/SOX complex in MHD patients. These constellations may result in an apparent reverse epidemiology in the form of protective features for obesity, hypercholesterolemia, and other surrogates of overnutrition. Diet and gene and their complex interaction may lead to a higher proportion of pro-inflammatory or oxidative lipoproteins such as HII, resulting in aggravation of the SOX and inflammatory processes, endothelial dysfunction, and subsequent atherosclerotic cardiovascular disease

and death in MHD patients. Both genetic polymorphisms as a result of survival selection of CKD progression and the imposed dietary restrictions to control hyperkalemia and hyperphosphatemia may play important roles in engendering and maintaining the KDW in MHD patients. Understanding the factors that modulate the KDW/SOX complex and their associations with gene, nutrition, and outcomes in MHD patients may lead to developing more effective strategies to improve outcomes in this and other 20 to 40 million Americans who also exhibit similar features such as individuals with heart failure, advanced age, terminal malignancy, AIDS, or cachexia. However, it is important to note that although SOX is often implicated as a main cause of the KDW, this relationship may not necessarily be causal and that SOX per se may be a consequence of the KDW. It is not clear which marker is a better surrogate of the KDW. More studies are needed to disclose the underlying pathophysiology of the KDW/SOX axis and its role in clinical outcome of the CKD patient population.

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