CPE Let Them Eat During Dialysis: An Overlooked Opportunity to Improve Outcomes in Maintenance Hemodialysis Patients

Kamyar Kalantar-Zadeh, MD, MPH, PhD,[*,†] *and T. Alp Ikizler, MD*[‡]

In individuals with chronic kidney disease, surrogates of protein-energy wasting, including a relatively low serum albumin and fat or muscle wasting, are by far the strongest death risk factor compared with any other condition. There are data to indicate that hypoalbuminemia responds to nutritional interventions, which may save lives in the long run. Monitored, in-center provision of high-protein meals and/or oral nutritional supplements during hemodialysis is a feasible, inexpensive, and patient-friendly strategy despite concerns such as postprandial hypotension, aspiration risk, infection control and hygiene, dialysis staff burden, diabetes and phosphorus control, and financial constraints. Adjunct pharmacologic therapies can be added, including appetite stimulators (megesterol, ghrelin, and mirtazapine), anabolic hormones (testosterone and growth factors), antimyostatin agents, and antioxidative and anti-inflammatory agents (pentoxiphylline and cytokine modulators), to increase efficiency of intradialytic food and oral supplementation, although adequate evidence is still lacking. If more severe hypoalbuminemia (<3.0 g/dL) not amenable to oral interventions prevails, or if a patient is not capable of enteral interventions (e.g., because of swallowing problems), then parenteral interventions such as intradialytic parenteral nutrition can be considered. Given the fact that meals and supplements during hemodialysis would require only a small fraction of the funds currently used for dialysis patients this is also an economically feasible strategy.

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Introduction

OVERNUTRITION IS A major problem in the general population and a serious risk of metabolic syndrome, cardiovascular disease, and chronic kidney disease (CKD), with subsequent increased death risk. However, in CKD patients, this relationship may be different, especially in those who undergo maintenance dialysis treatment. In the latter patient population, so-called "uremic malnutrition"[1] (or "malnutrition-inflammation complex"[2] or "renal cachexia"[3]), which is recently also referred to as "protein-energy wasting" (PEW),[4] is by far the strongest risk factor for adverse outcomes and death,[5] whereas surrogates of overnutrition such as obesity or hyperlipidemia appear counterintuitively protective.[6] Similar associations have been described in individuals with other chronic disease states such as heart failure[7] or in the geriatric populations.[8] It is believed that in CKD and other chronic diseases that are associated with wasting syndrome, pathophysiologic pathways related to malnutrition act as short-term killers and render such long-term killers as obesity or hypertension practically irrelevant. In other words, dialysis patients die much faster of short-term consequences of PEW so that they do not live long enough to die of the long-term consequences of overnutrition. This so-called time-discrepancy hypothesis[9] suggests that in CKD patients whose short-term mortality is high, interventions that can improve their nutritional status and prevent or correct wasting and sarcopenia have the potential to save lives.[10] In addition to longevity, nutritional status is a strong predictor of better health-related quality of life in dialysis patients.[11]

PEW and Mortality

If the PEW is such as strong death risk factor, one would expect that the PEW surrogates such as low serum albumin or lower protein intake correlate with mortality. Indeed, evidence suggests that they do. A low serum albumin concentration is by far the strongest predictor of mortality and poor

[*]*Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Medical Center, Orange, California.*

[†]*Fielding School of Public Health at the University of California–Los Angeles, Los Angeles, California.*

[‡]*Renal Division, Vanderbilt Medical Center, Nashville, Tennessee.*

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Address correspondence to Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine Medical Center, 101 The City Drive, Suite 400, Orange, CA 92868. E-mail: kkz@uci.edu

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Table 1. Suggested Intervention for Maintenance Hemodialysis Patients With Serum Albumin <4.0 g/dL or Other Signs of PEW

Oral Nutritional Interventions	In-Center, Intradialytic Administration	Advantages	Disadvantages
Meals during dialysis treatment	Preferred as routine for all hemodialysis patients	See Table 2	See Table 2
ONS	Preferred especially if meals not effective	See Table 2	See Table 2
Tube feeding (via temporary nasogastric tubing or PEG)	In- and off-center if oral nutrition not possible	Convenient access	Can only be used for fluid supplements
Parenteral			
IDPN	Preferred especially if albumin is <3.0 g/dL	Convenient	Offered only 3 times/wk
Total parenteral nutrition	Usually administered off-dialysis clinic	Can be used more frequently than IDPN	Requires an extra access line (e.g., PICC line)
Pharmacologic			
Appetite stimulators	To improve adherence*	Enhances protein/energy intake	May aggravate obesity; more fat accumulation than muscle?
Antidepressant	To improve adherence*	May improve appetite	Known side effects
Anti-inflammatory and/or antioxidative	To improve adherence*	May improve inflammatory/oxidative profile	Limited studies; unknown side effects
Anabolic hormones	To improve adherence*	May enhance muscle accretion rather than fat	Adverse events associated with anabolic steroid
Antimyostatin and/or other muscle-enhancing agents	To improve adherence*	May enhance muscle accretion	Limited human studies, unknown side effect profile
Other Interventions			
Dialysis technique	NA	Implemented as a part of routine treatment renovation	May cost more when compared with older techniques
Dialysis treatment factors	NA	Implemented during routine treatment	Costs/benefits should be weighed
Intradialytic exercise	Preferred	Improves muscle mass and function	Requires instrument provision and maintenance; technically might be challenging

NA, not applicable; PEG, percutaneous endoscopic gastrostromy; PICC, peripherally inserted central catheter.
*Not clear whether intradialytic (in-center) administration can offer any benefit beyond improving adherence to high-protein diet and supplements, including during hemodialysis therapy.

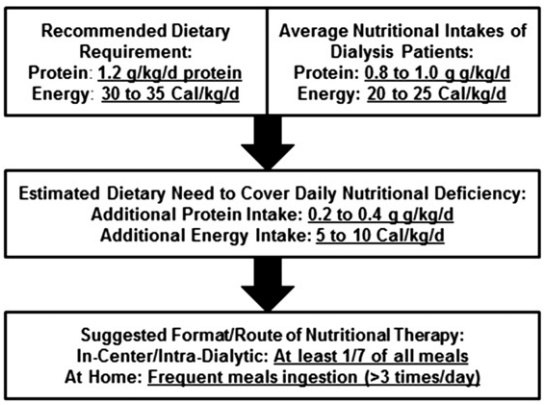

Figure 1. Justification of the additional need of dialysis patients for supplemented meals and nutrition.

outcomes in dialysis patients when compared with any other risk factors,[12,13] be it the traditional risk factors (hypertension, hypercholesterolemia, diabetes, obesity) or nonconventional ones (anemia measures, minerals and bone surrogates, dialysis treatment and technique).[5] The sensitivity of serum albumin to predict CKD patient outcomes is relatively high with such a granularity of as little as 0.2 g/dL or even smaller.[14–17] In other words, a dialysis patient with a baseline serum albumin of even 0.2 g/dL higher or lower than another patient with similar demographic and comorbidity constellations has a significantly lower or higher death risk, respectively. The albumin-death association is highly incremental and linear with virtually no cutoff level below or above which the association with survival would cease or reverse.[14,15] This is in sharp contradistinction to most other outcome predictors in CKD with U- or J-shape survival associations. Even more important to note is that changes in serum albumin over time are associated with proportional and reciprocal alterations in subsequent death risk in that a rise or drop in serum albumin by as little as 0.1 g/dL over a few month period is associated with improving or worsening survival, respectively.[14] Similar mortality predictabilities have also been reported with other nutritional markers such as serum prealbumin[18] (e.g., $<$30 mg/dL) and the "malnutrition-inflammation score" (MIS $\geq$ 5).[19] Nevertheless, serum albumin remains the simple single test that is readily available ubiquitously and has been recommended by most nutritional societies as a first-line nutritional marker. Hence, as shown in Table 1, a diverse array of nutritional and dietary interventions are often considered for maintenance hemodialysis patients with serum albumin less than 4.0 g/dL or other signs of PEW.

Meals and Oral Supplements During Hemodialysis Treatment

Given the exceptionally high dietary protein requirement of dialysis patients (~1.2 g/kg/day), and given the observation that most dialysis patients eat less than 1.0 g/kg/day of protein,[20] an average dialysis patient needs an additional 0.2 to 0.4 g/kg/day of protein supplement[21] (see Fig. 1). Inadequate food intake, especially during hemodialysis treatment days, is a common practice among U.S. dialysis patients, whereas in many other countries meals are routinely served during the hemodialysis treatment sessions. Table 2 summarizes some of the pros and cons pertaining to in-center (in the dialysis clinic) monitored eating and the provision of meals during hemodialysis treatments. In a recent online survey, when we asked nephrologists and dialysis centers in the United States as to why meal trays for patients do not exist during hemodialysis treatment, the common stated concerns include (1) postprandial hypotension; (2) risk of choking or aspiration; (3) infection control and hygiene issues, including fear of fecal-oral transmission of such diseases as hepatitis A; (4) staff burden and distraction; and (5) diabetes and phosphorus control (see Table 2).[21] It is not unusual to hear statements such as "They get food everywhere and this is not fair to the next patient that has to sit in their crumbs," "I don't want another lawsuit for choking while eating on dialysis" and "Having a full stomach might complicate their management."[22] On the other hand, meals are routinely given to dialysis outpatients in most European and Southeast Asian countries. German dialysis patients invariably eat during their hemodialysis treatments and have higher serum albumin and greater survival than their U.S. counterparts.[23] In the past, meals on dialysis were also routine in the United States. Indeed, a few Veteran Administration hospitals still provide meal trays, including breakfast, lunch, or supper, during all dialysis shifts, be it inpatient or outpatient.

Despite the traditional concerns of North American nephrologists and dialysis care providers, the positive development is that over the past few years increasing numbers of dialysis clinics have allowed and even encourage oral nutritional supplementation during the treatment. Indeed, several recent pilot and nonrandomized studies have indicated that provision of oral nutritional supplements with high protein content during hemodialysis has improved serum albumin.[24–27] Indeed, an elaborate metabolic study showed that oral protein intake during hemodialysis therapy is effective in opposing the catabolic effect of hemodialysis treatment that would otherwise last even hours after the therapy ended (Fig. 2).[24] We would also argue that in addition to improving nutritional status, providing in-center meals and/or oral nutritional supplements during hemodialysis treatment would improve patient compliance and satisfaction (Table 2). Patients may be more motivated to attend the treatments when they know that a lunchbox is awaiting them. Although in Europe meals on dialysis rarely lead to hypotension, we would argue that it can be considered as an effective strategy against intradialytic hypertension. Many patients may already ignore the eating-prohibitory regulations of some dialysis clinics and still bring in their own foods, including

Table 2. Pros and Cons of In-Center (in the Dialysis Clinic) Monitored Eating and Provision of Meals During Hemodialysis Treatments

Pros	Cons
Impact on nutritional status and clinical outcomes • Meals during HD are practiced routinely in many industrialized nations including Europe and Southeast Asia • Excellent survival in most countries where meals are served during HD • No major unfavorable outcomes reported in countries offering meals during HD	Low blood pressure and labile circulation during food ingestion • Blood pressure may be lowered during and after eating because of splanchnic circulation expansion even with new dialysis treatment and techniques • Hypotensive episode may lead to shortening dialysis treatment or less efficient fluid removal
Mitigates/corrects intra- and postdialysis catabolism • HD treatment exerts catabolic effects that can be avoided by eating during HD • Muscle wasting may be mitigated • Effectively increases the frequency of daily meal intakes	Risk of aspiration and other respiratory complications • Risk of choking is likely higher in patients with a history of neurologic disorders, swallowing problems, or other disabilities • Even in sitting position aspiration may happen in patient who cannot feed themselves at home
Better control of dietary phosphorus, potassium, salt, and fluid • In-center meals and supplements can be more optimally prepared for the specific needs of CKD patients • In-center meals may improve adherence to restricted salt and fluid intake • Intake of phosphorus binder can be monitored • Improved patient education can be achieved by simultaneous interaction with dietitian and nephrologist while eating	Infectious control and hygiene issues • Fecal–oral transmission of infection including hepatitis A possible • Food crumbs may lead to infestation • Risk if ingestion of rotten food and food poisoning is possible • Meal tray delivery and storage may pose additional hygiene challenges
Increased adherence with HD treatment • Increases the likelihood of attending HD treatment • May mitigate the likelihood of HD treatment shortening by hungry patients • Enhances communication among patients, dietitians, and other clinic staff	Burden on dialysis staff and logistics constraints • Overworked dialysis staff faced with additional responsibilities • Providing nutrition may not be regarded as an a justifiable part of patient care in dialysis clinics
Improved patient satisfaction and quality of life • In-center meals may make patients more content with dialysis treatment lifestyle • Improved quality of life by means of in-center meal may improve survival	Only a fraction of required meals are provided • Thrice-weekly meals account for 15% of all meals • The evidence that catabolic effect of HD can be mitigated or reversed by intradialytic nutrition is not convincing
Relatively low costs of meals on HD • The costs of providing in-center meals is a small fraction of expensive medications used in end-stage renal disease • Dialysis organizations can adapt this in the form of efficient and economical approaches	Added expenses to dialysis treatment • The costs of meals during dialysis may be small but still not negligible • If costs of meals are factored in by the insurance company or in the bundling equation, this may be at the cost of other more critical treatment components and medications

HD, hemodialysis.

ones with high phosphorus content and super-sized soft drinks. Hence, we are in the position to offer them a better and more appropriate food or supplement with higher protein content, lower phosphorus-to-protein ratio,[28] and lower potassium content.[29] The in-center food can be offered along with directly observed administration of phosphorus binder regimen and the required multivitamins at the time of meal or supplement intake.

There are several studies in which oral nutrition has been provided during hemodialysis treatment, including studies by Szklarek-Kubicka et al.[30] and Moreira et al.[31] In a more recent controlled trial known as the Anti-Inflammatory and Anti-Oxidative Nutrition during Dialysis (AIONID) study,[32] 84 adult hypoalbuminemic (albumin < 4.0 g/dL) hemodialysis patients were double-blindly randomized to receive 16 weeks of interventions, including oral nutritional supplement (ONS), pentoxifylline, ONS with pentoxifylline, or placebos, during hemodialysis treatments; these 4 groups were associated with an average change in serum albumin of $+0.21$ ($P = .004$), $+0.14$ ($P = .008$), $+0.18$ ($P = .001$), and $+0.03$ g/dL ($P = .59$), respectively. However, in a predetermined intention-to-treat regression analysis, only ONS during hemodialysis without pentoxifylline was associated with a significant albumin rise ($+0.17 \pm 0.07$ g/dL, $P = .018$).[32] In two recent large observational studies, ONS during hemodialysis was associated with improved survival[33] and improved hospitalization.[34] In another recent randomized controlled trial, the Fosrenol for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI) study[35] (ClinicalTrials.gov # NCT0111694110), in which 110 hypoalbuminemic (<4.0 mg/dL) hemodialysis patients received meals during hemodialysis for 8 weeks, the intervention group received high-protein meals as prepared meal boxes (50 g protein, 850 Cal, phosphorus-to-protein ratio < 10 mg/g) along with 0.5 to 1.5 g lanthanum carbonate

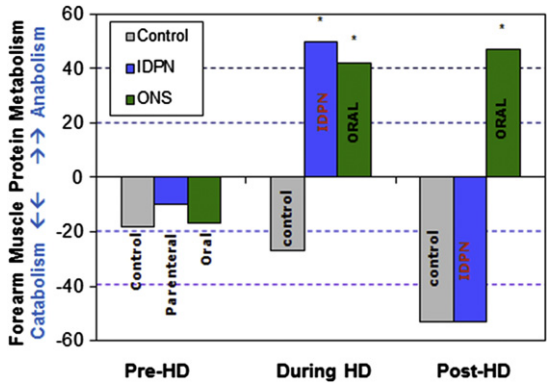

Figure 2. Anabolic effects of oral versus parenteral nutrition during hemodialysis treatment to justify preference for meals and oral supplements during hemodialysis treatment. Adapted from Kalantar-Zadeh et al.[21] and Pupim et al.[24]

(Fosrenol) titrated as needed to control phosphorus burden from the high-protein meals, whereas the control group received low-calorie (<50 Cal) meal boxes containing almost no protein (<1 g, such as salads) during each hemodialysis treatment. Among the 51 intervention and 55 control subjects who qualified for the intention-to-treat analyses, the combined rise in albumin of 0.2 g/dL or greater while maintaining phosphorus in the range of 3.5 to less than 5.5 mg/dL was achieved in 25.5% and 9.8%, respectively (χ^2 P value of .036). No serious adverse events were reported, and patients reported satisfaction with high-protein meals during hemodialysis.[35] Hence, in the FREDI study, provision of high-protein meals combined with a potent binder during hemodialysis treatment was safe and improved serum albumin while controlling serum phosphorus.[35] In summary, given the above studies, we suggest provision of maintenance meals (as in the FREDI study)[35] or balanced dietary supplement (as in the AIONID study)[32] during each and every hemodialysis treatment and dialysis clinic visit. A maintenance regimen can ensure adequate protein intake and reinforce similar dietary habits at home. We also recommend the frequent intake of a small amount of a protein-rich liquid oral supplement with prescribed pills to replace water, which is shown to improve outcomes in geriatric and nursing home patients.[36]

Other Nutritional Interventions

In addition to meals and nutritional supplements during hemodialysis, there are other potential interventions that can be used in conjunction or alone to improve the nutritional status of dialysis patients. These include, but are not limited to, appetite stimulators with or without antidepressant properties such as megesterol,[37] ghrelin,[38] and mirtazapine[39]; anabolic hormones such as testosterone and growth factors[40]; and antioxidative and anti-inflammatory agents such as pentoxiphylline and cytokine modulatory agents[41,42] or omega-3 fatty acid[43] (see Table 1). Intradialytic exercise with or without concomitant nutritional supplementation has been proposed as a potential therapy, although long-term efficacy of this strategy needs to be confirmed.[44,45] If more severe hypoalbuminemia (e.g., <3.0 g/dL) prevails that is not amenable to oral interventions even with adjunct pharmacologic therapy, or if a patient is not capable of receiving enteral interventions, parenteral interventions should be considered, such as intradialytic parenteral nutrition (IDPN).[46,47] IDPN is especially effective with such low serum albumin values.[48] Finally, non-nutritional interventions should also be considered, such as dialysis treatment modalities and techniques that lead to less inflammation or protein loss.[49,50]

Impact of Nutritional Interventions on Outcomes

An important question that is still unanswered is whether the PEW-albumin-death association a causal association (and amenable to interventions listed in Table 1) or an epiphenomenon? Whereas the debate continues as to how to find the correct answer to this question,[51-53] in our opinion a more clinically relevant and time-sensitive question is the following: "Can a nutritional intervention increase serum albumin in CKD patients and by doing so improve survival and quality of life?" We believe that the answer is positive on the basis of several experimental data,[48,54-59] although no single well-designed and well-performed randomized controlled trial with adequate sample size has been performed to date to answer this simple question. Indeed the entire field of nutritional support (e.g., in terminal cancer patients, postsurgical patients or geriatric or disabled populations) is based on the premise that independent of the cause of wasting and cachexia, provision of nutritional support improves patient's immediate and short-term outcomes or we would not be practicing it over the past few decades.[60] Whereas we do not deny the paucity of the controlled trials and the difficulties sounding the feasibility of nutritional interventions and testing their effects on hard outcomes,[61] it is our clinical and ethical opinion that keeping hemodialysis patients hungry during dialysis treatment is not an appropriate action.

Conclusion Remarks

There appears to be a consensus pertaining to the important role of favorable nutritional status in dialysis patient outcomes within the nephrology community. As we have moved toward longer hemodialysis sessions[62] and in anticipation of drastic changes in practice pattern and dialysis patient care in many countries, we need to rethink the pros and cons of provision of meals and oral supplements during dialysis treatment. Although this is a routine practice in Europe and most other countries, Northern American dialysis patients are deprived of nutritional intervention during dialysis. There is a consistent, strong, and robust association of nutritional status, and in particular serum albumin level, with survival in CKD patients along with data from several

studies indicating improvement in response to intradialytic nutritional supplementation. Hence, providing intradialytic meals or oral nutritional supplements to dialysis patients and other nutritional interventions are the most promising intervention to increase serum albumin and to improve longevity and quality of life in this patient population. Because provision of meals and oral supplements would require only a small fraction of the funds currently used for the expensive medications given to dialysis patients with no proven outcome modification, this is also an economically feasible strategy.[15]

Practical Application

Meals and oral supplements during hemodialysis treatment sessions may improve outcomes and offer more benefits than risks.

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