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REVIEW ARTICLE

CPE Eating During Hemodialysis Treatment: A Consensus Statement From the International Society of Renal Nutrition and Metabolism

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Poor nutritional status and protein-energy wasting are common among maintenance dialysis patients and associated with unfavorable outcomes. Providing foods, meal trays, snack boxes, and/or oral nutritional supplements during hemodialysis can improve nutritional status and might also reduce inflammation, enhance health-related quality of life, boost patient satisfaction, and improve survival. Potential challenges include postprandial hypotension and other hemodynamic instabilities, aspiration risk, gastrointestinal symptoms, hygiene issues, staff burden, reduced solute removal, and increased costs. Differing in-center nutrition policies exist within organizations and countries around the world. Recent studies have demonstrated clinical benefits and highlight the need to work toward clear guidelines. Meals or supplements during hemodialysis may be an effective strategy to improve nutritional status with limited reports of complications in real-world scenarios. Whereas larger multicenter randomized trials are needed, meals and supplements during hemodialysis should be considered as a part of the standard-of-care practice for patients without contraindications.

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Introduction

POOR NUTRITIONAL STATUS and protein-energy wasting (PEW) are common in patients undergoing hemodialysis (HD) treatment and are among the strongest predictors of poor outcomes in this population.[1-4] Because of these observations, there has been considerable effort to understand the optimal strategies to preserve and/or improve the nutritional status of these patients. A common choice among researchers and clinicians has been to provide food and nutritional supplements during treatment.[5,6] Allowing patients to eat during treatment helps offset reduced dietary intake observed on treatment days[7,8] and has had a positive impact on nutritional status[9-14] and, possibly, outcomes.[15,16] However, since postprandial hypotension, gastrointestinal (GI) symptoms, and reduced treatment efficiency have been reported this practice remains controversial.[5,6] Despite evidence for and against intradialytic nutrition (Table 1), numerous questions related to this topic remain unanswered. This ambiguity contributes to vastly differing policies related to in-center nutrition within dialysis clinics.[17,18] Providing answers to these questions could substantially improve patient care by informing the development of evidence-based guidelines. Therefore, the purpose of this review is to summarize the available evidence for each of these arguments and to highlight areas where additional research could clarify nephrology practice.

The Arguments in Favor of Intradialytic Nutrition

Nutritional Support During Treatment Improves Dietary Intake

Measures of nutritional status are among the strongest predictors of poor outcomes in patients undergoing HD treatment.[1-3] This relationship between nutrition indicators and outcomes is consistent across a wide range of measures. Because of the catabolic nature of HD treatment and the role of reduced dietary intake in the development of worsening nutritional status, patients undergoing HD have heightened requirements for both protein and energy.[19] Low serum albumin <4.0 g/dL by bromocresol green method (or <3.8 g/dL by bromocresol blue method) is among the strongest predictors of mortality and poor outcomes in chronic dialysis patients.[1] Hypoalbuminemia in dialysis patients can be a consequence of inadequate protein intake or inflammation.[20] A recent study in more than 30,000 HD patients showed that independent of the cause of hypoalbuminemia, higher dietary protein intake or an increase in protein intake over time is associated with higher levels of serum albumin or an increase in serum albumin over time (Fig. 1).[21] Hence, even if the cause of low serum albumin or PEW in

Table 1. Published Data Supporting Arguments for and Against Eating During Treatment

Evidence Supporting Eating	Evidence Against Eating
Reduced mortality • Reduced mortality in retrospective, observational studies in Ref.[15,16]	Postprandial hypotension • Increased hypotension observed in Ref.[22,23] • Decreased postprandial BP observed in Ref.[22-26] • Correlation between BP and eating in Ref.[27]
Improved nutritional status • Biochemical improvements in biochemical measures such as albumin and prealbumin.[9,11] • Nutritional reserve prevents acute catabolism associated with HD treatment.[13,14] Increased fat and lean mass.[12] • Dietary intake reduced in patients who do not eat during treatment.[7] Increased when providing meals.[8]	Reduction in treatment efficiency • Reduced Kt/V and URR observed in Ref.[26,28] and a transient reduction by UV absorbance in Ref.[29]
Patient adherence and satisfaction • Improved QOL observed in Ref.[30]	Gastrointestinal symptoms • ONS trials reported dropouts due to GI symptoms • Observed by clinicians.[18]
Provide more appropriate food choices • Observed in FrEDI trial.[9]	Aspiration • Cited in a small number of lawsuits as discussed by Ref.[31]
Reduced inflammation • Reductions in proinflammatory cytokines observed in Ref.[9,32]	Increased staff burden • Spills and pests not frequently observed by clinicians.[18]
Other • Improved blood glucose and educational opportunities cited reason for supporting in-center nutrition by dietitians.[17]	Food safety • Infections not frequently observed by clinicians.[18]

BP, blood pressure; FrEDI, Fosrenol for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients; GI, gastrointestinal; HD, hemodialysis; ONS, oral nutrition supplement; QOL, quality of life; URR, urea reduction ratio; UV, ultraviolet.

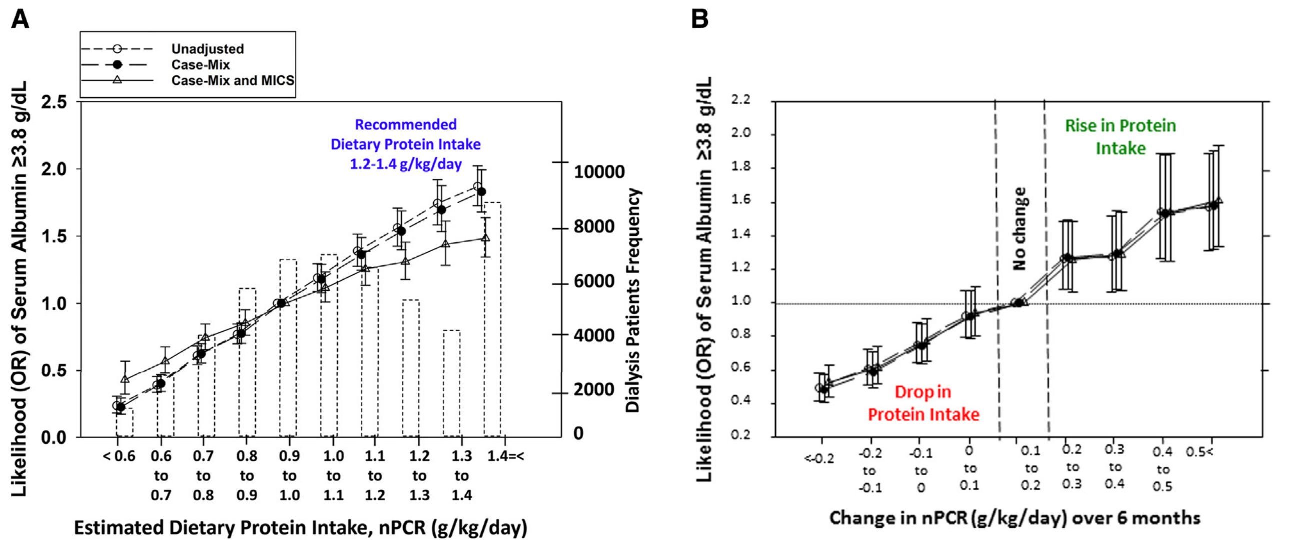

Figure 1. Association of estimated dietary protein intake, represented by normalized protein catabolic rate (nPCR) and higher likelihood, represented by larger odds ratio (OR), of serum albumin ≥3.8 g/dL among 36,757 incident hemodialysis patients in a large USA dialysis organization over 5 years (January 2007 to December 2011): (A) Higher nPCR is associated with higher likelihood of serum albumin ≥3.8 g/dL. (B) An increase in nPCR over 6 mo is incrementally associated with higher likelihood of serum albumin ≥3.8 g/day, whereas a decline in nPCR over time is associated with lower chance of serum albumin ≥3.8 mg/dL.These figures are adapted, with permission, from data by Eriguchi et al.[21]

dialysis patients is not inadequate food intake, it may be feasible to improve PEW and to correct hypoalbuminemia by providing higher protein intake. In fact, it is estimated that ∼10,000 lives could be saved each year if serum albumin could be effectively increased in US dialysis patients.[1]

Despite the suggestion of a strong association between PEW and mortality in dialysis patients, data show that many HD patients do not meet the International Society of Renal Nutrition and Metabolism recommendations for protein intake of >1.2 g/kg/day.[7,33] Among the most frequently cited barriers to adhering to the high-protein diet are a lack of time[34] and the restrictive nature of the renal diet.[35,36] Policies that restrict eating during treatment may exacerbate these barriers and may help explain why patients who do not eat during treatment have intakes that are further reduced on treatment days.[7,37] Consistent with the hypothesis that missed meals and lack of time are limiting factors in achieving appropriate dietary intake, providing meals during HD treatment has been shown to increase overall intake as well as the percentage of patients who meet dietary requirements.[8]

Providing Nutrition During HD Treatment Improves Nutritional Markers and Quality of Life

Providing meals and other nutritional support during HD treatment has been shown to improve a variety of nutritional markers. Nutritional support provided during treatment ameliorates acute protein catabolism associated with a single HD treatment (Fig. 2).[13,14] In addition to these short-term benefits, intradialytic nutrition over prolonged periods of time is reported to increase fat and lean mass,[12] possibly physical function,[32] inflammation,[9,32] biochemical measures (such as albumin and prealbumin levels),[9,11] and more integrated measures such as subjective global assessment.[10] In addition to these reported improvements in nutritional status, intradialytic nutrition[30] including eating foods during HD[9] (Rhee and Kalantar-Zadeh, personal communications) might improve quality of life, which may help to explain why some patients

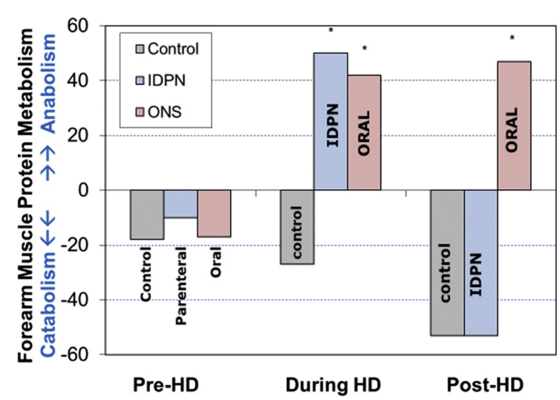

Figure 2. Providing nutritional support during hemodialysis (HD) treatment can prevent muscle catabolism associated with a single hemodialysis therapy. Anabolic effects of oral vs. parenteral nutrition during hemodialysis treatment to justify preference for meals and oral supplements during hemodialysis treatment. IDPN, intradialytic parenteral nutrition; ONS, oral nutrition supplement.This figure is adapted from Pupim et al.[13,14]

choose to eat even when this practice is discouraged by clinic staff.[31]

Additional Benefits of Intradialytic Food Intake

A number of additional benefits to providing nutrition during HD treatment have been proposed.[5,6] These include educational opportunities for dietitians, improved blood glucose control, better HD treatment adherence, reduced hospitalizations, and increased satisfaction with dialysis. Most of these potential benefits are supported by minimal data or have not yet been studied.[38] It has also been suggested that providing nutrition during treatment may provide an incentive for more appropriate food choices. The recently published "Fosrenol for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI)" trial, in which patients consumed high-protein meals that are consistent with renal guidelines during HD treatment, supports the feasibility of this practice.[9] In this trial, 110 adults undergoing thrice-weekly HD treatment and in whom serum albumin was <4.0 g/dL (bromocresol green) were randomly assigned to receive either high-protein (50-55 g protein and 400-500 mg phosphorus) meals during dialysis combined with lanthanum carbonate or a low-protein (<1 g protein and <20 mg phosphorus) meal during dialysis. Among 106 participants who satisfied the trial entrance criteria, 27% ($n = 15$) and 12% ($n = 6$) of patients in the high-protein versus low-protein HD meal groups, respectively, achieved the primary outcome (intention-to-treat P-value = .045). A lower proportion of patients in the high-protein versus low-protein intake groups experienced a meaningful rise in interleukin-6 levels: 9% versus 31%, respectively ($P = .009$). No serious adverse events were observed although the study has been criticized by Agarwal et al.[39] for lack of intradialytic blood pressure (BP) data. Hence, in hypoalbuminemic HD patients, high-protein meals during dialysis combined with lanthanum carbonate are safe and increase serum albumin without increasing phosphorus.

Providing Nutritional Supplements During HD Treatment Is Associated With Reduced Mortality

Other data suggesting possible benefits of intradialytic oral nutrition (IDON) are observational studies of intradialytic supplementation programs and mortality in malnourished HD patients.[15,16] Lacson et al.[16] performed an observational study examining outcomes in a patient population who were propensity score matched and received either an oral nutritional supplement or served as a control. Patients who received supplements had lower mortality in both the intention-to-treat (after adjustment) and the as-treated models. Similarly, in patients from a different dialysis provider, Weiner et al.[15] found reductions in mortality in both the intention-to-treat and as-treated models. It is important to note that these latter studies were not randomized and were retrospective, and the risk of inadvertent bias is substantial. For example, physicians who aggressively provide nutritional support to patients with PEW, in comparison to physicians who do not provide nutrition to such patients, might be expected to more aggressively diagnose and treat other medical disorders. Clearly, randomized prospective controlled clinical trials are needed to test whether nutritional support to prevent or treat PEW will reduce morbidity, mortality, or improve quality of life.

Why Intradialytic Nutrition?

Although intradialytic nutrition including meals during HD has been reported to improve intake, nutritional status, and mortality, a major question that needs to be answered is whether intradialytic nutrition is superior to providing similar support outside of dialysis treatment. There are many reasons to believe that timing is an important factor in providing nutrition support to patients undergoing HD treatment. HD is a catabolic procedure, and repeated exposures to this stimulus may contribute to a loss of protein mass and functional capacity.[40] Approximately, 10 to 12 g of amino acids (AA) and several grams of peptides are removed during each HD treatment.[41-43] Providing nutritional support during treatment has been shown to prevent the catabolism associated with a single treatment (Fig. 2).[13,14] A potential mechanism for this anti-catabolic benefit is the maintenance of circulating and intracellular AA at a time when they would normally be depleted by HD. Another benefit of maintaining circulating AA is that this may prevent protein carbamoylation, an irreversible process that can damage proteins and lead to the development of comorbidities, especially those related to cardiovascular disease.[44]

Timing may also be an important factor in achieving adequate dietary intake. While decrements in nutritional status are frequently the result of a complex disorder,[45] 1 of the components of this disorder is an inadequate intake of dietary protein and energy. Providing meals or nutritional supplements during treatment could help add to, rather than replace, dietary intake that would otherwise occur outside of the clinic,[46] especially in patients with early satiety.[47,48] This would result in higher overall dietary intake that may help offset reductions in nutritional parameters.

The Arguments Against Intradialytic Nutrition

Hemodynamic Instability Is the Most Frequently Cited Reason to Restrict Nutrition During Treatment

The most frequently cited reason to restrict intradialytic nutrition is hemodynamic instability.[17,18,39] Eating results in a reduction in total peripheral resistance (TPR) and accompanying increase in splanchnic and hepatic blood

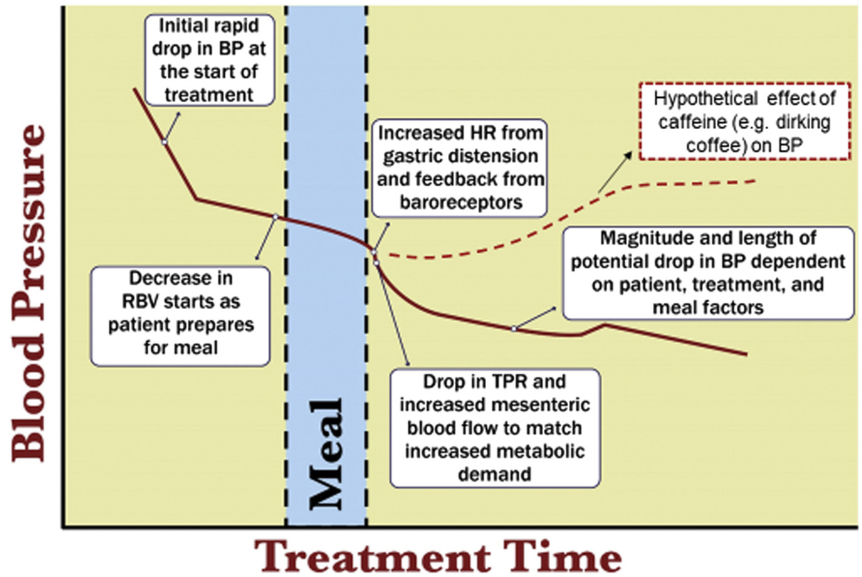

Figure 3. Potential influence of eating during hemodialysis on blood pressure (BP). A decrease in RBV followed by a reduction in total peripheral resistance (TPR) lead to drop in BP. Note the hypothetical scenario of simultaneous caffeine intake, for example, by drinking coffee, on maintaining or even increasing BP. *HR*, heart rate; *RBV*, relative blood volume.

flow.[49] In healthy adults, this reduction in TPR is countered by an increase in cardiac output, driven primarily by gastric and other pressor responses (Fig. 3). In certain populations, such as the elderly, diabetics, and/or patients with autonomic dysfunction, this response may not be adequate to offset the drop in TPR resulting in a reduction in BP.[50] It has been hypothesized that hypovolemia may worsen the balance between reductions in TPR and cardiac compensation.[51,52] Consistent with this hypothesis, Kistler et al.[5] have reported that there was generally a transient reduction in BP in trials examining intradialytic nutrition.

A concern with intradialytic nutrition is that any additional drop in BP accompanying eating could exacerbate common symptoms patients experience during HD treatment including cramping, headaches, and nausea. If severe enough, these symptoms could cause shortened treatment times leading to reductions in the delivered dialysis dose.[26] These symptoms could also be detrimental to the patient, as they may reflect ischemia in susceptible organs including the heart, brain, and intestine.[53-55] Even in the absence of overt symptoms, there is growing evidence that ischemic damage to these tissues occurs during treatment.[56] Although there is limited evidence that eating may be associated with hypoxia,[57] it could be hypothesized that the heart may be particularly susceptible to postprandial ischemia due to the potential for a simultaneous increase in heart rate and drop in diastolic BP.[22,23] Furthermore, Meyring-Wösten et al.[58] that reported intradialytic hypoxemia was associated with inflammation and higher all-cause hospitalization and mortality. Taking these factors into account, current European Best Practice Guidelines suggest that the benefits and risks of food intake during HD should be weighed against the nutritional status of the patient.[59]

Limited Data on the Role of Intradialytic Nutrition in the Development of GI Complications

The second most frequently cited reason to restrict intradialytic nutrition is the risk for GI symptoms.[18] Although frequently treated as a separate issue, some GI complications, particularly abdominal pain, may be a sign of reduced blood flow and oxygen delivery to the digestive tract.[60] Outside of clinician opinion, there are very little systemically collected data about the effect of eating during HD treatment on GI symptoms. A few studies reported GI complications after the consumption of an oral nutrition supplement during or immediately before treatment[61,62] that resulted in the exclusion of a small number of patients. However, in other hemodynamically unstable patient populations, there is some evidence that providing nutrition support can improve intestinal tissue oxygenation, barrier function, and outcomes.[63-65] This would raise the possibility that IDON could offset (or potentially exacerbate due to the increased metabolic demand) intestinal ischemia associated with treatment.[66] Whereas this area certainly warrants further research, we currently do not believe that meals during dialysis should be abandoned or restricted for this reason in patients who do not suffer GI distress during or immediately after nutritional intake.

In-Center Meals May Reduce Solute Removal

It has also been suggested that allowing patients to eat during HD may reduce the efficiency with which solutes are removed by sequestering blood in the digestive tract or shortening treatment time due to symptom development.[26,29] Studies that have examined this potentially negative aspect of eating during HD have produced equivocal results.[26,28,29] In 2 studies, authors found a lower urea reduction in treatments in which patients consumed a meal during treatment.[26,28] However, concerns have been raised over using urea removal as a measure of efficiency when also feeding protein.[67] In a separate study, solute removal was measured using ultraviolet (UV) absorbance of the dialysate, ionic dialysance, and dialysate collection (urea, uric acid, and creatinine) during a single treatment in which patients consumed a meal. After the meal, the authors observed a transient reduction in solute removal as measured by UV absorbance, but no changes in removal were observed during the meal when measured using ionic dialysance or dialysate collection. This led the authors to conclude that the transient reduction measured by UV absorbance may be the result of UV absorbing solute appearance after eating and not the result of an actual reduction in clearance. Given the findings of these studies further work is necessary to determine the role of in-center nutrition in solute removal.

Additional Concerns Related to Intradialytic Nutrition

Additional concerns, such as both hyperglycemia and reactive hypoglycemia,[68] potential access damage,[17] increased staff workload, impaired hygiene and microbial contamination, and financial constraints are supported by minimal evidence or have yet to be studied.[5,6,18] Finally, a sporadically reported complication is choking or aspiration when eating during dialysis.[31] We argue that the risk of aspiration in the dialysis center is not any higher than the risk when hospitalized patients receive a meal tray. In the latter instance, patients are often unobserved, whereas, in the dialysis unit, patients are under almost constant observation by nurses and other healthcare workers.

Prevalence of Adverse Events Is Largely Unknown

One of the most challenging aspects in weighing the evidence related to eating during HD is that there are currently not enough data on the prevalence of adverse events associated with eating during treatment. Clinicians who propose that patients should be allowed to eat during treatment will suggest that these adverse events are rare, citing the large number of clinics and patients around the world who eat during treatment without reports of adverse events. Indeed, we found that many clinicians who allow patients to eat during HD treatment had not experienced the negative sequelae often attributed to IDON.[18] Similarly, a number of recent studies where patients were fed meals during treatment have reported the patients experienced no serious adverse events.[8,9] It

Table 2. Practical Guidelines for Eating During Treatment

Practical Guidelines for Eating During Treatment
Provision of meals during hemodialysis treatment should be the default practice and standard-of-care in all dialysis centers.
• Hemodialysis patients should consider eating during treatment if they
○ are hemodynamically stable
○ have no contraindiction for eating during hemodialysis (see in the following)
Patient characteristics
• Patients should consider eating outside of treatment if they
○ have low blood pressure during treatment
○ frequently coughing or risk of choking
○ undergoing current bout of diarrhea that can be aggravated by eating
○ prone to stomach pain, indigestion, nausea, or vomiting during treatment
○ diagnosed autonomic dysfunction that may be precipitated by eating
Position
• Patients should be encouraged to eat in an upright position
Food characteristics
• Risk of hypotension may be greater with
○ larger meals
○ high amounts of simple carbohydrates
○ hot as opposed to cold food
○ lack of caffeinated items such as coffee
• Patients should be encouraged to choose foods
○ high in protein and low in phosphorus (phosphorus to protein ration $<$15 mg/g)
○ fit within the renal diet
○ do not increase choking risk
○ do not increase thirst
○ do not need to be stored, chilled, or prepared in-center
○ can be eaten with 1 hand
○ will not make a mess
○ do not have a strong odor
• Patients should be prepared to take phosphorus binder with food
• Patients should strive to avoid large variations in intake from treatment to treatment

should be noted, however, that these studies may have enrolled healthier patients who are hemodynamically stable and that there are reports of lawsuits concerning aspiration caused by choking associated with eating during dialysis treatment.[31] Systemic collection of data on the frequency of adverse events associated with eating during dialysis is an important step toward evidence-based policy decisions.

Practical Aspects of Implementation

Cost

The cost of providing meal trays or oral nutritional supplements during treatment is often cited as a barrier. However, recent trials have demonstrated that both meals and supplements can be provided at a relatively low cost.[9,32] This is especially true when oral nutritional interventions are compared with intradialytic parenteral nutrition or to pharmacologic treatments that are frequently carried out despite equivocal data on efficacy. Furthermore, modeling suggests that the costs of providing supplements to malnourished patients might be partially offset by reduced treatment costs.[69]

Eating Is an Umbrella Term and Not All Foods or Supplements Are Created Equal

Although "eating" is frequently grouped together as a single phenomenon, the degree to which the cardiovascular system might be challenged by dietary intake is influenced by many characteristics of the items consumed (Table 2). For example, size,[70] nutrient composition,[71] and temperature[72] of the meal have all been shown to have a significant influence on postprandial hemodynamics. For instance, taking caffeinated drinks during HD might attenuate the drop in BP after eating (unpublished data from K.K.-Z) as it has in other populations.[73,74] However, this is controversial, and an antihypotensive effect of caffeine during HD was not observed in 1 trial during HD.[24] In addition, the time of day and interval of time since a patient last ate have also been observed to influence the pressor response.[50] There are many factors related to the treatment itself that have been hypothesized to influence the hemodynamic response including the ultrafiltration rate, the length of time into the HD session when the nutrition is consumed, and whether ultrafiltration is adjusted for dietary intake. Most trials examining postprandial hemodynamics during HD have used solid, mixed-macronutrient meals.[5] An important question to those who support IDON should be which sources of nutrition will maximize benefits and minimize the potential for hemodynamic instability or other adverse events.

Influence of Timing During HD

Many trials examining the benefits or potential risks of eating during HD have chosen to provide food or nutritional supplements toward the beginning of HD because of the perception that patients may experience greater problems when eating later in the treatment. However, a recent trial[75] found no difference in nausea or vomiting when providing a meal in the first or second hour of treatment. Clear methodology about the timing of oral nutrition supplement and meals may help to more clearly answer this question moving forward.

Eating During Treatment May Not Be Appropriate for All Patients

Finally, it is likely that the risks and benefits of eating during HD may differ among individual patients in this era of personalized or precision medicine. The default for many clinics has been to adopt a "one approach fits all" policy. It is important for experts and opinion leaders on both sides of the argument to acknowledge that future policies may benefit from additional nuances. For example, when we reviewed trials examining postprandial hemodynamics, trials that did not select hemodynamically stable patients appeared to be associated with greater drops in BP or hypotensive episodes after eating.[5] In addition, trials have also found numerically greater drops in BP in patients with impaired autonomic function.[22] On the other hand, most of the benefits associated with eating during treatment have been shown in patients who were already malnourished, and further research should help to clarify whether the benefits of eating during treatment are worth the potential risks for patients who may not currently be classified as PEW or malnourished.

Conclusion

Allowing patients to eat regular food or consume nutritional supplements during HD has been associated with improvements in nutritional status, quality of life, and possibly clinical outcomes. Despite these improvements and despite its routine practice in many industrial nations such as Germany, France, and the United Kingdom, this practice remains controversial in some other countries including the United States because of concerns that include postprandial hemodynamics, adverse GI symptoms, decreased treatment efficiency, and increased clinician workload. This has led to vastly differing policies concerning feeding during HD around the world, within countries, and even within HD providers within the same country. Because of the limited number of published studies on this topic, much of this debate is based on anecdotal data. Many questions remain unanswered including a comparison between nutritional support during and outside of treatment, an understanding of the actual rate of adverse events, the clinical benefits of such treatments, the effect of meal/supplement composition on benefits and risks, and patient characteristics that may influence safety. Answering these questions could help organizations develop evidence-based policies that will improve patient care. Current evidence suggests that the provision of meals or nutritional supplements during HD treatment is an effective strategy to improve nutritional status with limited reports of complications. Whereas larger multi-center randomized controlled trials are needed to better examine outcomes, nutrition during dialysis should be considered as a part of the standard-of-care practice for hemodynamically stable patients who have no contraindications and no history of intolerance to consuming food during treatment.

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