

ACUTE EFFECTS OF INTRADIALYTIC NUTRITION SUPPLEMENTATION ON
HEMODYNAMICS, TREATMENT EFFICIENCY, AND GASTROINTESTINAL
SYMPTOMS IN MAINTENANCE HEMODIALYSIS PATIENTS

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2015

Urbana, Illinois

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ABSTRACT

Poor nutritional status is common and among the strongest predictors of mortality in patients undergoing maintenance hemodialysis (HD) treatment. Reduced dietary intake, especially on days in which patients undergo treatment, is one factor that contributes to this poor nutritional status. Providing nutritional supplements or allowing patients to eat during HD treatment can help restore dietary intake, improve nutritional status, and significantly reduce mortality in malnourished patients. However, in the United States this practice is frequently restricted due to concerns about patient safety.

To better understand practice patterns related to eating during HD treatment we conducted an international survey. We received 73 responses representing clinics in six continents. Among this cohort, 61 of 73 clinicians (85%) were at clinics that allowed patients to eat during treatment and 53 (73%) were at clinics that provided food during treatment. Interestingly, none of the nine clinics from North America provided food during treatment. In the second part of this survey, we asked the 61 clinicians who were at clinics which allowed patients to eat during treatment about their experience with the six most-cited reasons to restrict eating during treatment using a four point scale. Clinicians responded that they observed choking (98%), reduced Kt/V (98%), infection control issues (96%), spills or pests (83%), gastrointestinal issues (71%), and hypotension (62%) either “rarely” or “never.”

The results of our survey suggested that gastrointestinal (GI) issues were amongst the conditions most frequently attributed to eating during HD treatment. However, there have been no studies directly examining the effects of providing nutrition on these symptoms. One reason for this lack of data may have been the absence of a validated tool to measure GI symptoms. Therefore, we developed and validated a questionnaire to measure GI symptoms associated with

a single HD treatment. Following a brief face validation with renal dietitians, we recruited 50 maintenance HD patients and administered our survey following a mid-week HD treatment. During the same treatment we measured dietary intake by diet recall. Three weeks later we repeated this process. In general, we found good agreement between items in each domain and repeatability among individual domains. Prevalence of GI symptoms during treatment (77.1%) was much higher than previously reported and associated with the intake of fat ($r=.318$, $p = 0.027$) and fiber ($r=.386$, $p = 0.007$) during treatment.

At the same time as our validation study, we also sought to determine the effect that liquid supplements had on the symptoms commonly associated with eating during treatment. We used a within-subjects design ($n=8$) to compare standard HD treatment (HD) to a standard HD treatment in which patients ingested 30 grams of whey protein starting 30 minutes into their treatment (HD + Protein). We found no interaction between groups in any hemodynamic variable ($p>0.05$). However, there was a main-effect of time for a reduction in SBP, decrease in heart rate, and a trend for a reduction in MAP. Furthermore, there was no difference in the reduction ratio of β 2-microglobulin, reduction ratio of urea, GI symptoms, or symptomatic hypotension between the two treatments ($p > 0.05$ for all). These data suggest that 30 grams of whey protein by itself does not exacerbate symptoms during HD treatment.

However, carbohydrates and lipids have been previously implicated as the primary cause of postprandial drops in blood pressure and GI symptoms during hemodynamic instability. Therefore, we applied the same within-subjects model to test for the effect of a renal specific mixed-macronutrient supplement. We baseline tested 11 HD patients to determine cardiovascular structure and function. Following baseline testing, we monitored a standard HD treatment (HD) and a standard HD treatment in which patients consumed a nutrition supplement (HD + ONS).

HD + ONS resulted in a trend for an increase in blood glucose ($p = 0.061$) compared to HD. Despite this increase in glucose, a potentially vasoactive compound, we found no interactions among any hemodynamic variable ($p > 0.05$ for all) in the HD + ONS compared to HD. While there were no interactions, postprandial beat-to-beat cardiac output and heart rate were elevated in the HD + ONS group compared to the HD group ($p < 0.05$) over the 150 minutes following supplementation. In spite of these hemodynamic alterations, we found no statistical difference between any measure of treatment efficiency or GI symptoms between HD and HD + ONS ($p > 0.05$ for all). When we compared the maximum change in BP following ONS with treatment characteristics, cardiovascular structure, and cardiovascular function, we found only baseline baroreceptor sensitivity was associated with the change in MAP ($r=0.706$, $p=0.05$).

In conclusion, we tested the effects of two liquid nutritional supplements on three of the main reasons cited by clinicians to restrict intradialytic nutrition. We found no difference in blood pressure, treatment efficiency, or GI symptoms with either supplement. However, we did find an elevated cardiac output and heart rate following the consumption of a mixed-macronutrient supplement. Future work should continue to evaluate factors related to safety of intradialytic nutrition, especially the effect of different supplements on local postprandial hemodynamics, gut barrier function, and intestinal ischemia. However, our data do not support the frequent practice of restricting intradialytic nutrition.

ACKNOWLEDGMENTS

I will forever be grateful for the opportunity to join Ken's lab. Ken gave me the chance to find my own way in academia while still providing the guidance necessary to complete these projects. In addition to Dr. Wilund's valuable insight, I am also extremely grateful to Dr. De Lisio, Dr. Chapman-Novakofski, Dr. Heffernan, and Dr. Ikizler for their valued input throughout this process.

None of this would have been possible without the members of the Wilund lab. Harry, Eliza, Emily, Sush, Rebecca, Kyle, Mason, Hank, Jen, and Luis were incredibly supportive in my development. I was also lucky to experience my entire five years with two of the greatest lab-mates imaginable, Jinny and Peter. I am especially appreciative of Annabel who was involved in every aspect of these projects and supported me in every way possible throughout this process. Additionally, I am very grateful to Kristin, Courtney, Barb, and Beth who went above and beyond their job descriptions to keep everything in our laboratory running smoothly, and thank you to Linda, Tina, Julie, Aaron, and the entire Freer Hall staff who did the same for the entire department.

I am extremely grateful to the Renal Research Institute, the clinic staff, and especially Dr. Kotanko, Dr. Raimann, and Deborah Fairrow, who supported our research throughout the years. Debbie, Mary, Becky, and Maria for including me in their survey work. This work would not have been possible without the generous financial support of The American Heart Association. And above all, this research would not have been possible without the amazing patients who were willing to participate in each of our studies. It is my hope that these projects will improve the quality of your daily lives.

Most of all thank you to my family. I am lucky to have such a supportive network. Without your unconditional support, I would have never pursued this challenge and I definitely would never have finished. Thank you Mom, Dad, Brian, Kathy, Virginia, Ernie, Betty, Jack and all of my extended family for your support.

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CHAPTER 1

INTRODUCTION

Nutritional status is among the strongest predictors of poor outcomes in HD patients independent of whether it is measured by dietary intake [1, 2], body size [3], biochemical indicators [4, 5], or more comprehensive scoring systems [6]. One factor that contributes to poor nutritional status in patients undergoing maintenance HD is inadequate dietary intake [7, 8]. This inadequate intake is further reduced on days in which patients undergo treatment [8]. Allowing patients to eat or consume nutritional supplements during a single treatment can help maintain intake [8, 9], attenuate inflammation [9], and prevent muscle catabolism [10-12]. Continuing to provide nutritional supplements during treatment improves nutritional markers in the blood [13], body reserves [14-16], and subjective global assessment [15]. All of these improvements may contribute to the reduction in mortality that has been observed when providing intradialytic nutrition to malnourished patients [17, 18].

Despite the well documented benefits, providing nutrition during HD treatment is controversial. Many reasons have been proposed to restrict intradialytic nutrition [19], but very few of these reasons have actually been examined [20]. This has led to clinic practices that vary widely throughout organizations, regions, and the world [21]. The most studied of the potential risks associated with eating during treatment is hemodynamic instability. Previous trials have produced mixed result, but in general have found a transient reduction in BP after eating that has not resulted in symptomatic hypotension [20]. However, these trials have also been surprisingly uniform in that they have enrolled hemodynamically stable patients and fed large, solid, mixed-macronutrient meals.

Liquid nutritional supplements represent an alternative to solid meals. Among clinicians, there is a perception that these supplements may be less hemodynamically challenging and therefore, many clinics have adopted different policies related to providing intradialytic nutritional supplements as opposed to solid food. Certainly arguments could be made to support these notions, as liquid supplements cause gastric distension which results in a well-documented gastric pressor response that helps maintain postprandial BP. However, liquid supplements also empty more quickly from the stomach, which is a key determinant of both the magnitude and duration of postprandial drops in BP.

Therefore, we set out to determine the effect of two different liquid nutritional supplements on symptoms commonly associated with eating during HD treatment. In our first study, we chose to use a supplement containing protein because of both its documented benefits when provided during HD and its smaller hemodynamic alteration compared to the other macronutrients. Due to previous reports demonstrating minimal hemodynamic changes following protein ingestion, we hypothesized that this supplement would not lead to changes in hemodynamics or symptoms compared to a standard HD treatment. In our second study, we chose to use a renal specific mixed-macronutrient supplement. These supplements have previously been shown to be the preferred supplements of maintenance HD patients. Given the addition of carbohydrates and lipids, we hypothesized that this would lead to a transient reduction in BP, but not be associated with increased symptoms. We believe that understanding the postprandial response, especially to different types of food and supplements, is an important step to the widespread utilization of intradialytic nutrition and the first step towards the development of standardized clinical recommendations for this important practice.

CHAPTER 2

RETHINKING THE RESTRICTION ON NUTRITION DURING HEMODIALYSIS TREATMENT

Introduction

The annual mortality rate for maintenance hemodialysis (MHD) patients in the United States (U.S.) is nearly 20%, a rate that is higher than nearly every other industrialized country in the world [22]. This disparity in mortality rates has been attributed to many factors including, but not limited to, patient demographics and certain clinical practices. With reference to the latter, an obvious difference between hemodialysis (HD) treatment in the U.S. and elsewhere is that patients in the U.S. are often not allowed to eat while dialyzing. Providing nutrition during dialysis has been shown to be effective in improving whole-body protein balance and attenuating hemodialysis-related inflammation without obvious metabolic complications [19, 23]. Recent data also suggests that intradialytic nutrition supplementation is associated with better survival in MHD patients [17, 18].

Despite its well-documented advantages, intradialytic feeding is heavily restricted in the U.S., primarily due to concerns that eating during HD may exacerbate hypotensive events during the treatment. Additionally, reduced dialysis efficiency and exacerbation of gastrointestinal symptoms are also frequently cited as reasons to restrict intake during HD (Table 1) [24-26]. These concerns, however, may be somewhat exaggerated and could be detrimental, as restricting nutrient consumption during HD contributes to increased protein breakdown [11, 27] and

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worsening nutritional status, further predisposing MHD patients to increased risk of morbidity and mortality [28].

Nutritional status is an important predictor of outcomes in MHD patients

HD, while life-saving, is a highly catabolic condition. It is estimated that 18-75% of MHD patients may suffer from protein-energy wasting (PEW) [29]. MHD patients can lose between 1-3 kg of lean mass per year [30], leading to significant reductions in physical function, fitness, and activity [31]. This shift towards a frail phenotype with worsening nutritional status is also associated with reduced quality of life [32], increased hospitalizations [33], and mortality [34]. The relationship between nutrition status and outcome is consistent across a wide range of nutritional markers including biochemical indicators [4, 5, 35], nutritional intake [1, 2], and nutritional reserve (fat and lean mass) [28]. These findings suggest that nutrition status may be an appropriate target to improve outcomes in this population.

Recommended protein and energy intake in MHD patients

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend increased caloric and protein intakes (35 kcal/kg/day and 1.2g/kg/day, respectively) for MHD patients [36]. These elevated intakes may be difficult for patients to reach due to a variety of barriers including dietary restrictions, anorexia, and socio-economic limitations [37]. Indeed, many patients fail to comply with these recommendations as evidenced by large clinical trials, such as the HEMO study, in which cohorts were significantly below the KDOQI guidelines [38]. Furthermore, research has shown that dietary intake is lower on treatment days as compared to non-treatment days. This is especially true in patients who do not eat during their treatment [38],

suggesting that the intradialytic window may be an important therapeutic target to improve dietary nutrient intake.

Eating during dialysis is restricted in most US clinics

Despite the benefits specific to providing intradialytic nutrition (reviewed in [19, 23]), eating during HD has remained a topic of debate for many years within the field of nephrology [24-26]. Eating during HD treatment is restricted in many clinics in the U.S., despite being allowed or even encouraged, in many other countries. Surprisingly, very little research has assessed many of the proposed risks of eating during dialysis (Table 1). Instead, many of the concerns are based on anecdotal evidence from clinical practice, which may be subject to impact bias and should be investigated in well-controlled trials. The following sections will highlight the current state of evidence regarding the proposed risks of eating during dialysis, with special attention given to effects on blood pressure regulation and intradialytic hypotension, as this is a primary reason cited for the eating restrictions.

Table 1. Proposed Advantages and Disadvantages to Intradialytic Nutrition

Proposed Advantages	Proposed Disadvantages
Reduced Mortality	Postprandial hypotension
Improved nutritional status	Reduction in efficiency
Patient adherence and satisfaction	Gastrointestinal symptoms
Educational opportunity	Hygiene
Improved blood glucose control	Increased staff burden
Provide more appropriate food choices	Financial constraints
Reduced inflammation	Aspiration

Intradialytic hypotension: A common complication of HD treatment

Intradialytic hypotension (IDH) is the most common adverse event during HD treatment, with an estimated prevalence of 5 to 40% of all treatments [39-42]. IDH may be either symptomatic or asymptomatic. Symptomatic IDH generally meets three criteria: 1) an abrupt fall in blood pressure (BP); 2) symptoms such as cramping, headaches, nausea and vomiting; and 3) requires medical intervention [43]. Symptomatic hypotension is a major concern because it is both uncomfortable and dangerous for the patient. Oftentimes, symptomatic hypotension requires the ultrafiltration rate to be decreased, or very rarely the treatment to be stopped altogether. Interventions to treat symptomatic IDH include administration of mannitol and saline, which increase the osmolarity of the blood and expand plasma volume. These interventions, however, cause significant thirst between treatments, contributing to high interdialytic fluid gains that further increase the risk of IDH in the subsequent HD treatment [44]. Chronic fluid overload during the interdialytic period and hypotension during treatment are believed to contribute to a gradual impairment of cardiac function [45]. These factors may contribute to the strong relationship between IDH and poor outcomes in MHD patients [46].

Eating during dialysis and blood pressure

There is a concern that eating during HD may exacerbate the decline in BP that typically occurs during treatment, leading to greater incidence of IDH [47]. While eating is typically not associated with a drop in blood pressure in healthy young adults [48], in certain populations such as those with insulin resistance, the aged, or those with autonomic dysfunction, eating may result in a postprandial drop in BP [49]. Epidemiologic studies have identified a number of risk factors that may contribute to excessive drops in BP following eating (reviewed in [50]). These factors

include excessive blood pooling in the splanchnic region, reduced baroreflex function, inadequate sympathetic neural drive, release of vasodilatory molecules during digestion, and hypovolemia. Any of these factors may contribute to a drop in BP following eating, and are primary concerns for potential causes of IDH following intradialytic nutrition.

Studies examining the effect of eating during HD treatment on BP and hemodynamics

Observational studies

Two observational studies have reported on the association between intradialytic eating, drinking, and BP. The largest study was a retrospective chart review of habitual intake and BP over three treatments in 126 stable MHD patients [51]. No correlation was found between oral intake and any measure of BP. Furthermore, there was no difference in oral intake between days where IDH occurred or did not occur ($p=0.93$). In contrast, a second observational study investigated the relationship between habitual nutrient intake during MHD and IDH in 23 patients over 166 total treatments [52]. Although the overall incidence of events was quite low (13 total mannitol events), hypotension ($SBP < 90$ mm Hg) occurred more often when patients consumed more than 200 kcal during treatment ($p < 0.001$), and the use of mannitol was higher in the group that consumed greater than 200mL of fluid ($p < 0.014$). Despite these hemodynamic differences there was no difference in symptoms such as cramping. These equivocal findings may be the result of many differences in methodology. Most notably, the latter investigation did not select stable patients and may highlight that food intake is better tolerated in those patients who are stable.

Interventional studies

The suggestion that eating during MHD treatment results in a significant reduction in BP was first put forward 3 decades ago by Sherman et al [53] who studied 9 non-diabetic MHD patients prospectively over 125 dialysis treatments. In half of these treatments (n=62), patients were given a standard meal halfway through their dialysis treatment. One year later, Zoccali and colleagues undertook a similar study in 13 patients [54]. Both of these studies found an acceleration in the drop in BP, a transient reduction in BP, and an increase in symptomatic hypotension in the time following the meal. However, the applicability of these studies to current treatment may be limited by differences in treatment parameters including dialysis membrane, dialysate, and the use of acetate as a buffer, which has been shown to increase the risk of developing hypotension [55].

Following this initial work demonstrating postprandial reductions in BP during HD treatment, work shifted towards examining the mechanism for these changes. Given the compounding influence of eating and ultrafiltration on blood volume, hypovolemia has been a common target. Sivalingham and colleagues gave 20 stable MHD patients a standard meal 45 minutes into their HD treatment. The rate of change in relative blood volume (RBV) increased in the postprandial state compared to pre-meal values. These changes coincided with a significant reduction in mean arterial pressure (MAP) 30 minutes after food intake (91 ± 19 vs. 86 ± 20 mm Hg, $p = 0.04$). Similarly, Shibagaki and colleagues found a postprandial reduction in RBV preceding changes in BP suggesting a possible role of RBV and hypovolemia in the postprandial drop in BP [56].

The Shibagaki study also allowed a unique opportunity to compare the effects of patient position on hemodynamic response [56]. Sixteen of 21 patients received a standard meal during

dialysis in the supine position and six in the seated position (one received in both). RBV dropped less in patients who were in the supine compared to the seated position (Seated -28.21 ± 2.41 vs. Supine $-13.99 \pm 0.91\%/hr$). Similarly, systolic blood pressure (SBP) and diastolic blood pressure (DBP) dropped compared to the pre-meal values in patients who received the meal in the seated position (152/85 to 143/79 mmHg), but only DBP was reduced in patients in the supine position (138/78 to 137/71 mmHg). Although differences in RBV and BP in patients in the supine position were minimal compared to those in the seated position, this observation suggests that reductions in venous return may play a role in the drop in BP some patients experience following eating and warrants further examination.

Barakat and colleagues further examined the mechanism behind hemodynamic adaptations to food ingestion [57]. To accomplish this, they maximized hypovolemic stress by distributing ultrafiltration over only the first two hours of treatment; feeding a standard meal after the first hour. Within this context, they found eating caused a significant reduction in MAP as a result of reduced systemic vascular resistance and lack of increase in cardiac output. These findings supported a previous hypothesis that the drop in blood pressure as a result of intradialytic feeding was the result of increased blood flow to the digestive system, lowering of peripheral resistance, and lack of cardiac compensation [58]. However, these mechanistic studies also raise many important questions including the influence these adaptations have on central BP, symptom development, and the influence of meal or supplement composition on these hemodynamic adaptations.

Finally, in recent years two larger studies have emerged examining the hemodynamic response to eating during HD [59, 60]. Kara and Acikel fed 25 stable patients a standard meal and witnessed a transient reduction in BP but no difficulties with symptomatic hypotension.

Similarly, Müller-Deile and colleagues conducted a study to examine the influence of eating during HD on hemodynamics and treatment efficiency [59]. Forty stable MHD patients were fed a standard meal during treatment. They found no reduction in SBP, DBP, or MAP following meal ingestion ($p > 0.05$ for all vs BP before eating) further suggesting that eating is generally well tolerated, especially in stable MHD patients. Future work should attempt to determine what differentiates patients who may experience a drop in BP following eating.

The effect of eating during treatment on solute removal

Another proposed consequence arising from eating during treatment is a reduction in the efficiency with which solutes are removed during treatment. Two main mechanisms have been proposed to explain why intradialytic food consumption may reduce the efficiency of HD treatment [60]. The first, although not documented in the literature, is that patients will discontinue treatments early due to discomfort caused by the reduction in BP. This shortened treatment time would lead to a reduction in solutes removed by dialysis. The second mechanism proposes a reduction in solute removal due to sequestration of blood in the digestive tract, minimizing the blood available to be dialyzed and reducing the concentration gradient between the blood and dialysate.

Studies examining the effect of eating on dialysis efficiency

Several studies have examined the influence of eating before or during HD on treatment efficiency. Singri and colleagues compared the efficiency of a single dialysis treatment following a three hour fast to that of a meal two hours prior to the start of dialysis [61]. The meals were variable, but all contained at least 0.4 g of protein per kilogram of body weight. They found that

efficiency, as measured by urea reduction ratio (URR) and single pool Kt/V, was not reduced as a result of eating a meal prior to the start of the treatment. Eating prior to the start of HD is unlikely to lead to the circulatory changes or early treatment termination hypothesized to contribute to a reduction in efficiency.

To more appropriately address these concerns, two studies have measured the effect of intradialytic food consumption on efficiency using urea kinetics. Kara and Acikel examined the effects of eating during dialysis on treatment efficiency (N = 25) [60] by comparing a standard HD treatment with one where patients were given a standard meal. Similarly, San Juan Miguelsanz et al. [62] assessed patients during standard dialysis in which they were allowed to eat, followed by restricting intradialytic food intake the following week. In both the study by Kara and Acikel (URR 67.8 ± 6.1 vs. 72.1 ± 0 , $p < 0.001$; Kt/V 1.4 ± 0.2 vs. 1.6 ± 0.2 , $p < 0.001$) and San Jaun Miguelsanz (URR (71.5 ± 5.92 vs. 73.5 ± 6.61 , $p = 0.057$ and Kt/V 1.54 vs. 1.65 , $p < 0.05$) efficiency was reduced in the treatment in which patients ate. However, the interpretation of these studies is limited by the possible confounding effects of protein metabolism on estimated urea removal. In fact, it has been hypothesized that if urea modeling was applied to this data to account for the protein patients consumed, the efficiency of these treatments may actually have improved [63].

Using different methodology, Müller-Deile and colleagues further examined the effect of eating during HD on treatment efficiency [59]. They continually monitored treatment efficiency by both UV absorbance and dialysate collection. Efficiency, as measured by UV absorbance, but not dialysate clearance, was transiently influenced by eating. Potential explanations for the transient reduction in efficiency with UV absorbance include increasing solute appearance due to rapid absorption or release from other compartments. The combination of results from these

studies suggest that observed reductions in measurements of efficiency may be the result of increased appearance rather than reduced clearance, and the clinical significance of these reductions is limited. This argument is furthered by recent evidence from our laboratory suggesting that reduced treatment efficiency is not commonly experienced by practitioners who allow patients to eat during treatment (Kistler et al., manuscript in preparation).

Studies examining the effects of eating during HD on GI symptoms and other concerns

Of the remaining concerns to restrict intradialytic eating (Table 1), gastrointestinal (GI) symptoms are the most frequently cited by practitioners. MHD patients have a greater prevalence of GI symptoms than the general population [64, 65], and these symptoms are inversely associated with serum albumin and quality of life [64]. Nausea and vomiting are common in patients with kidney disease possibly due to delayed gastric emptying [66], although many other factors are likely to contribute. GI symptoms, including nausea, are thought to occur acutely during 10-15% of all treatments [67-69]. Nutritional supplementation studies that have tracked GI symptoms have reported incidences similar to [14, 70], or below [71] these estimates. However, to our knowledge there are currently no studies directly examining the effects of eating during HD on GI symptom amount or severity and trials are needed to determine if eating increases the incidence of these symptoms.

Summary of Current Findings

Hemodynamic complications are the most commonly cited reason to restrict intradialytic nutrition. Previous studies have demonstrated that eating during treatment causes a transient drop in BP. However, there is limited evidence that this transient drop in BP translates to clinically

significant increases in symptomatic hypotension in patients undergoing MHD, especially in the era of bicarbonate-based dialysate [59]. This observation is further supported by the large number of intradialytic supplementation studies that have not observed hemodynamic complications. Many questions related to hemodynamic stability following intradialytic eating remain unanswered, such as understanding the role of meal composition and the presence of underlying cardiovascular complications on the risk of developing IDH. Additional research is needed to help outline best practices and to determine ways to minimize patient risk.

Treatment efficiency is the most studied of the remaining concerns about eating during HD. However, many of these studies are confounded by the effect of protein metabolism on urea kinetics. Furthermore, the modest and sometimes transient reductions observed in treatment efficiency may not be clinically relevant. Therefore, it remains unclear if eating has any significant influence on treatment efficiency. To our knowledge, other arguments against eating during dialysis treatment such as food safety, staff burden, pest control, and choking or aspiration have not been studied. Future studies should address these issues so practitioners can make more informed decisions regarding patient feeding practices during treatment.

Conclusions

MHD treatment is a catabolic procedure with significant adverse consequences including muscle wasting, reduced quality of life, and a number of metabolic alterations. Recent evidence shows intradialytic nutrient supplementation represents a clinically and financially feasible strategy to improve nutrition status. Available data indicate that while eating during HD treatment does generally cause a transient reduction in BP, it is tolerated by a vast majority of patients without significant clinical consequences. While further research may demonstrate

strategies to reduce the potential risks associated with eating during treatment, the widespread use in multiple countries without reports regarding its complications suggests that intradialytic nutrition is an appropriate strategy to improve clinical outcomes in a large proportion of the MHD patient population who can tolerate it.

CHAPTER 3

TO EAT OR NOT TO EAT-INTERNATIONAL EXPERIENCES WITH EATING DURING HEMODIALYSIS TREATMENT

Introduction

Maintenance hemodialysis (HD) is a highly catabolic condition. Poor nutritional status is common in HD patients [29] and is associated with reduced quality of life [32], increased hospitalizations [33], and increased mortality [34]. Providing patients with supplemental nutrition during a single HD treatment increases skeletal muscle protein synthesis, reduces catabolism, and improves net protein balance [11, 12, 72]. Long-term provision of nutrition during HD treatment has been shown to increase nutritional indicators such as albumin [13], lean mass [16], and subjective global assessment [15] as well as quality of life [73]. These improvements in nutritional status may contribute to the recent observation that intradialytic oral nutrition supplementation programs are associated with significant reductions in mortality [17, 18].

Despite these benefits, many clinics do not allow patients to eat during HD treatment. Many reasons have been proposed to restrict patients from eating during HD, including hemodynamic instability, choking risk, and reductions in dialysis efficiency, among others [19, 24, 25]; however, these concerns are primarily anecdotal as there is little evidence in the published literature supporting them. The lack of research on this topic may contribute to varying clinical practices [74]. Furthermore, differences in clinic practices on eating during treatment

Reprinted from Journal of Renal Nutrition, Volume 24, Authors: Kistler BM, Benner, D, Burgess, M, Stasios, M, Kalantar-Zadeh, K, and Wilund KR, Title: To eat or not to eat: international experiences with eating during hemodialysis treatment, Pages 349-352, Copyright (2014) with permission from Elsevier.

have been suggested to contribute to the global disparities in albumin and other nutrition indicators [19, 75]. Describing international clinic practices is an important step to better understand worldwide differences in nutritional outcomes and determine best practices. Therefore, we set out to perform a survey to describe international practices on eating during treatment and to provide insight into clinical experiences with eating during treatment.

Methods

We developed an 11 item survey about clinic practices and clinician experiences related to eating during HD treatment. This survey was developed based on a combination of clinical experience and review of the literature [19, 24, 25]. Demographic data for each participant was also collected. The survey was distributed to attendees during the 2014 International Society of Renal Nutrition and Metabolism Conference in Wurzburg, Germany [76]; all attendees were encouraged to respond. Collected surveys were analyzed and entered into SPSS version 22 (Chicago, IL). Partial responses were included in the overall analysis. Data are reported as the number of respondents and the percent of categorical responses. A chi-square test (χ^2) was used to determine practice differences between clinic settings. Significance was set using an alpha of 0.05. However, no additional statistical comparisons were performed due to the limited number of responses. Finally, qualitative data were analyzed, clustered, and summarized.

Results

We received 73 responses from six continents (Africa (3, 4.1%), Asia (7, 9.6%), Australia (5, 6.8%), Europe (39, 53.4%), North America (9, 12.3%), South America (10, 13.7%)). Clinicians who responded to the survey were dietitians (71.2%), nephrologists (26.0%),

or clinical researchers (2.7%) who worked in units housed within a hospital (63.0%), outpatient clinic (45.2%), and/or an academic setting (16.4%).

Clinic practices for eating during hemodialysis treatment are summarized in Figure 1. Fifty-three clinics (72.6%) served food other than supplements during HD. Forty-nine of the 53 clinics who served food during treatment (92.5%) provided food at no cost to the patient. However, none of the nine clinics from North America provided food during treatment. Clinics that were in a hospital setting were more likely to provide food to patients during treatment than those that were not associated with a hospital ($\chi^2 = 3.84$, $p = 0.05$). Qualitative analysis of clinician responses showed that clinics providing food were generally providing full meals that tended to be high in carbohydrates. In addition, tea or coffee was often included as a beverage.

Forty-seven clinicians responded that their clinics (64.4%) provided supplements during treatment. Forty-three of the 47 (91.5%) provided these supplements at no cost to the patient. Outpatient clinics were less likely to provide nutritional supplements during treatment compared to clinics who were not described as outpatient ($\chi^2 = 4.35$, $p < 0.04$). Clinics tended to provide patients with liquid as opposed to solid supplements. These supplements were most often commercially-available mixed macronutrient supplements.

We also asked clinicians about their experiences with eating during treatment. When asked whether four specific factors influenced their decision to allow patients to eat, clinicians responded that they allowed patients to eat in order to provide additional energy (88.7%), teaching opportunities (46.8%), better control of blood glucose (32.3%), and difficulty enforcing a no eating policy (16.1%). Additionally, clinician open-ended responses included: patient quality of life, providing protein, barriers to intake outside of the clinic (i.e., lack of cooking skills, transport time, socio-economic limitations, etc.), clinic culture, and nutrient timing.

Finally, we asked clinicians about six commonly-cited reasons to restrict feeding during HD. Clinician responses are summarized in Table 2. In general, clinicians did not frequently experience these proposed consequences of eating during treatment. In addition to these commonly cited reasons, clinicians also indicated that staff workload, difficulty overcoming clinic culture, cost, and patients' forgetting binders as reasons to restrict eating during HD treatment.

Table 2. Clinician experiences with six commonly cited reasons to restrict eating during hemodialysis treatment.

	Never	Rarely	Sometimes	Often
Postprandial Hypotension (n=53)	18 (34.0)	15 (28.3)	18 (34.0)	2 (3.8)
Gastrointestinal Symptoms (n=52)	14 (26.9)	23 (44.2)	15 (28.8)	0 (0.0)
Reduced Treatment Efficiency (n=45)	42 (93.3)	2 (4.4)	1 (2.2)	0 (0.0)
Spills or Pests (n=46)	31 (67.4)	7 (15.2)	5 (10.9)	3 (6.5)
Choking (n=46)	39 (84.8)	6 (13.0)	1 (2.2)	0 (0.0)
Infection Control Issues (n=46)	42 (91.3)	2 (4.3)	2 (4.3)	0 (0.0)

Discussion

We conducted a survey examining the practices and experiences of clinicians related to eating during HD treatment at the International Society of Renal Nutrition and Metabolism Conference in Wurzburg, Germany. Our primary findings from this survey include the following: 1) eating during dialysis is commonly allowed and frequently encouraged by clinics throughout most of the world; 2) many clinics provide food and supplements to patients at no-cost; 3) providing additional energy appears to be the primary reason that clinics allow or

encourage patients to eat during treatment; and 4) many of the proposed negative sequelae of eating during HD are not commonly observed in clinical practice. To our knowledge this is the first published study to describe international practices related to eating during treatment.

Understanding the variability in clinic guidelines is an important step to outlining best practices. We observed that most clinics around the world allow, encourage, and in many cases, provide food at no-cost to patients. However, none of the nine clinics from North America provided patients with food. This supports previous reports indicating that practices related to eating during treatment in North America, particularly the U.S., appear to be more restrictive [19]. While the current study is underpowered to make statistical comparisons between continents or countries, this observation deserves further examination. Though speculative, this difference in clinical practice may contribute to the observation that patients' albumin levels tend to be lower, and mortality rates higher, in the U.S. compared to the rest of the world [75].

Another interesting observation was that the food being provided to patients was high in carbohydrates. This is important given our finding that approximately 37% of clinicians have observed hypotension at least “sometimes.” Carbohydrates have been shown to lead to a disproportionate postprandial drop in blood pressure compared to the other macronutrients [77], although this effect has not been demonstrated in patients undergoing HD. In addition, protein appears to be more effective at preventing HD-associated catabolism and inflammation [11, 12] and may lead to fewer hemodynamic complications. Further research may be warranted to determine the optimal food choices during HD treatment.

We also asked clinicians about their experiences with patients eating during HD treatment. These clinical experiences contribute important evidence to the debate within the nephrology community about the best practices related to eating during treatment [19]. Providing

additional energy was the primary reason that clinics allowed patients to eat during treatment. When asked about six commonly-cited arguments for restricting eating during HD treatment, clinicians reported that the majority of these concerns occurred “rarely” or “never.” The most frequently reported consequence of eating during treatment was intradialytic hypotension. This is consistent with previous observations that eating during treatment causes a transient reduction in blood pressure, but is generally well accepted in stable patients (Kistler et al., manuscript in preparation). Describing the frequency and individual circumstances with which these symptoms occur will help clinicians make informed decisions regarding practices in this controversial area.

A primary weakness of this study was that the data was obtained from a convenience sample of clinicians attending a renal nutrition conference. These practitioners are likely to have greater interest in nutrition and may have more progressive policies in their clinic related to eating during HD treatment. In addition, this survey was written in English which may have limited the participation of non-native English speaking participants. We also did not receive an adequate number of responses to statistically compare continents. Despite this limitation, the group as a whole has provided valuable insight into clinical experiences with eating during treatment. Additionally, this research has raised important questions about differences in practice around the world and how these may contribute to global disparities in nutritional status and outcomes.

In summary, our results indicate that eating is common during treatment in many countries around the world, disparities may exist in global practices, and most of the proposed negative sequelae of eating during HD are not commonly observed in clinical practice. These data describe current nutrition practices, provide a potential contributor to global differences in albumin, and highlight the need for more research to inform decisions regarding eating during

HD. Specifically, future research should be conducted to further characterize and evaluate international differences in eating practices, to examine the prevalence and severity of proposed consequences associated with eating during treatment, and to find ways to minimize patient risk.

Practical Applications

This study suggests that many of the proposed negative consequences associated with eating during treatment are not commonly observed by practitioners in the clinical setting. This observation should provide insight into current practices and highlight the need for future research in this controversial area of practice.

Acknowledgments

The authors would like to thank the International Society of Renal Nutrition and Metabolism for allowing us to distribute our survey at their conference.

CHAPTER 4

A SCALE TO MEASURE GASTROINTESTINAL SYMPTOMS ASSOCIATED WITH A SINGLE HEMODIALYSIS TREATMENT: VALIDATION AND ASSOCIATION WITH INTAKE DURING TREATMENT

Introduction

Gastrointestinal (GI) symptoms are a common problem in ESRD patients [64, 65] and are inversely associated with serum albumin and quality of life [64]. Many factors may contribute to the high prevalence of GI symptoms in ESRD patients including uremia, delayed gastric emptying, and medications [66]. In addition to the uremic syndrome, the dialysis procedure itself may exacerbate these symptoms. Patients undergoing hemodialysis (HD) have significantly more GI symptoms than patients undergoing peritoneal dialysis [78]. These differences are especially pronounced in relation to abdominal pain, diarrhea, and constipation; symptoms that are consistent with the acute development of hypotension and mesenteric ischemia [79]. Furthermore, GI symptoms are among the most common complications of HD treatment [67-69] suggesting that these acute GI disturbances may contribute to the chronic differences in GI symptoms between dialysis modalities and therefore may be an important target for intervention.

Despite these observations, there is limited data on GI symptom development during HD treatment. Previous data on this topic has been almost exclusively based on single-item questions which can be unreliable [80] and limited in scope to questions about nausea [67-69]. Furthermore, there is a lack of data on the relationship between different treatment practices and GI symptom development. One such practice, eating during treatment, has frequently been restricted in part due to the hypothesis that it may contribute to GI symptom development [19].

However, there are no trials specifically examining the relationship between eating during HD treatment and GI symptom development. A tool specifically designed to measure GI symptoms associated with a single HD treatment may add to the depth of knowledge on this topic and allow for the comparison of treatment practices. Therefore, the purpose of this study was to develop and validate a tool to measure acute GI symptoms associated with a single HD treatment and to assess the relationship between GI symptoms and intradialytic nutrient intake in maintenance HD patients.

Methods

We modified the American version of the Gastrointestinal Symptom Rating Scale (GSRS) [81] to measure GI symptoms associated with a single HD treatment. The GSRS contains 15 questions in five domains (Abdominal Pain, Reflux Syndrome, Indigestion Syndrome, Diarrhea Syndrome, and Constipation Syndrome) scored on a seven point Likert scale (1=no symptoms and 7=very severe symptoms, Appendix 1). This version was modified by changing the wording of the questions within three domains (Abdominal Pain, Reflux Syndrome, and Indigestion Syndrome) to ask specifically about the time during a single HD treatment. Wording of the remaining two domains (Diarrhea Syndrome and Constipation Syndrome) were altered to ask patients about the time immediately following the specific HD treatment until the start of the following treatment.

We sent this modified version of the GSRS to five renal dietitians around the country for comment. Comments received more than once were discussed by the authors and considered for inclusion. Based on these expert comments, one additional modification to the wording in the questions was adopted.

Following this initial validation, we recruited 50 maintenance HD patients from clinics in central Illinois. One patient received a kidney transplant and one patient was unavailable for follow-up, leaving us with 48 HD patients completing all time points. At the end of a mid-week HD session, patients were asked about the symptoms they experienced (Abdominal Pain, Reflux, and Indigestion) during that specific treatment. During this same HD treatment, dietary intake was measured with a diet recall using the USDA 5-pass method along with visual inspection of items including cups and wrappers. At the start of the following treatment (48-72 hours later), participants were asked about symptoms from the final two domains (diarrhea and constipation) that they had experienced since the end of the previous treatment. Three weeks later this protocol was repeated to determine the repeatability of measures.

Data were entered into SPSS version 22. Internal consistency of each of the five domains was analyzed using Cronbach's alpha. To determine repeatability, the correlations between GI symptom domains during the first and second treatment were analyzed using Pearson correlations. Prevalence of GI symptoms associated with a single HD treatment was determined by the proportion of participants with an average score greater than 1 on all of the questions within an individual domain of the first GSRS. GI symptoms in patients who ate during treatment (Average energy intake > 0 kcal) and those who did not eat during treatment were compared using independent samples t-test. Finally, the GSRS and dietary recall from the first and second treatment were averaged and the relationship between nutrients of interest and GI symptoms were determined using additional Pearson correlations. When outliers were present, we re-ran our correlations after removing outliers. Outliers were identified by the method suggested by Hoaglin [82]. In short, we extended the values at the 25th and 75th percentile by a

value 2.2 times the difference between the values at each of those quartiles. Significance for all analyses was set at an alpha of 0.05.

Results

Forty-eight HD patients completed the entire study protocol and were included in the analysis (Table 3). Internal consistency and repeatability of the five domains are presented in Table 4. The internal consistency of the indigestion domain was improved by removing the question on burping. Therefore, the burping question was removed for all subsequent analyses.

Table 3. Demographics for maintenance hemodialysis patients included in validation study.

Demographics	Value
Age (Years)	56 ± 13
Vintage (Months)	53 ± 59
Gender (Male/Female)	30/18
Race (%)	
African American	54.2
Caucasian	45.8
Hispanic (%)	8.3
Diabetes (%)	54.2
Smoke (%)	20.8
Digestive Disorder (%)	18.8

The prevalence of GI symptoms during a single HD treatment (generalized score greater than 1) was 54.2% (mean generalized score, 1.60 ± 0.74), 43.7% (1.48 ± 0.67), and 6.2% (1.07 ± 0.31) for the abdominal pain, indigestion, and reflux domains respectively. In the time following a specific mid-week HD treatment, 41.7% (1.73 ± 1.24) and 45.8% (1.72 ± 1.09) reported a

generalized score greater than 1 for the diarrhea and constipation syndrome respectively.

Combined 77.1% of HD patients experienced symptoms in at least one domain. However, the severity of symptoms was quite low with a mean score of less than 2 for all domains.

Table 4. Reliability and repeatability of the GSRS to measure acute gastrointestinal symptoms associated with a single hemodialysis treatment.

Scale	Cronbach's Alpha	Correlation between repeated measures (p – value)
Abdominal Pain	.676	0.329 (0.022)
Indigestion Syndrome	.515	0.437 (0.002)
Reflux Syndrome	-.052	0.708 (<0.001)
Diarrhea Syndrome	.852	0.459 (0.001)
Constipation Syndrome	.778	0.645 (<0.001)
Indigestion (Burping Removed)	.631	0.415 (0.003)

There was no significant difference in GI symptoms ($P>0.05$ for all) among patients who ate ($n=32$) versus those who did not eat ($n=16$) during treatment. However, there were significant correlations between dietary intake during treatment and GI symptom domains (Table 5), including correlations between the intradialytic intake of fiber, fat, and the severity of indigestion during the treatment (Figure 1). However, when outliers for fat and fiber intake were removed, these correlations were no longer significant ($p>0.05$).

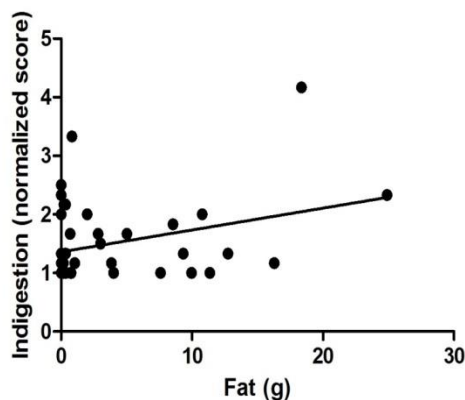
Table 5. Average dietary intake during hemodialysis treatment and its association with gastrointestinal symptom severity measured by the GSRS.

Nutrient	Amount	Stomach Pain	Indigestion Syndrome	Reflux Syndrome	Diarrhea Syndrome	Constipation Syndrome
Energy (Kcal)	112.72 ± 158.52	0.060	0.237	0.056	0.024	0.021
Protein (g)	6.97 ± 8.84	-0.046	0.162	0.070	0.134	0.124
Carbohydrate (g)	14.57 ± 22.62	0.082	0.192	0.050	-0.025	-0.056
Fat (g)	3.25 ± 5.68	0.050	0.318*	0.049	0.016	0.075
Sodium (mg)	121.60 ± 329.83	0.078	0.208	-0.027	0.078	-0.19
Fiber (g)	0.38 ± 0.81	0.132	0.386*	0.028	0.076	0.135
Sugar (g)	8.06 ± 13.21	0.033	0.075	0.035	-0.116	-0.136
Fluid (g)	207.09 ± 171.16	0.130	0.148	-0.096	-0.087	-0.047

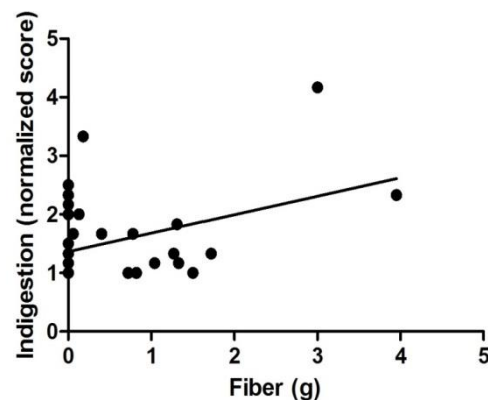
*p<0.05

Figure 1. Association between intake of nutrients and severity of indigestion during hemodialysis treatment.

a.



b.



Relationship between mean fat (a) and fiber (b) intake during hemodialysis treatment and the severity of indigestion experienced during hemodialysis treatment.

Discussion

We modified a version of the GSRS to measure GI symptoms associated with a single HD treatment. In general, this modified tool was internally consistent and repeatable in this population of maintenance HD patients. When we used these multi-item scales to measure GI symptoms associated with a single HD treatment, we found the prevalence of GI symptoms during treatment to be higher than previously reported. Although GI symptoms were quite prevalent, the severity of these symptoms was low. Finally, we found that the consumption of fat and fiber during HD treatment was associated with GI symptom severity.

In general, we found good agreement between the individual items within each domain in our modified version of the GSRS. The one exception was the reflux domain. This was likely due to the small number of patients (6.2%) who experienced reflux during treatment and may not speak appropriately to the level of agreement between items. One possible explanation for the low number of patients experiencing reflux is that all of the patients in the current trial were seated during treatment, which may reduce reflux [83]. Given the relatively high prevalence of reflux in the HD population (24.2%) [78], it is likely that it may be more prevalent in clinics where HD is performed in a different position. Similar to the data on agreement, we also found significant correlations between repeated measures among each of the domains. Combined these findings suggest that our modified version of the GSRS is an internally consistent and reliable tool for measuring GI symptoms associated with a single HD treatment.

The development of GI symptoms is a frequent complication of HD treatment. Previous trials have found that patients develop symptoms in approximately 10-15% of all HD treatments. However, these trials have relied on single item questions and have primarily asked only about the development of nausea. Similar to these previous trials, we found that approximately 16% of

patients experienced nausea during a single HD treatment. However, when we used a multi-item tool to ask about symptoms within five domains associated with a single treatment, we found that 77.1% of HD patients experienced symptoms in at least one domain. This is a rate considerably higher than previous reports. Furthermore, the prevalence and severity of acute symptoms measured over a single HD treatment were quite similar to previous studies which have asked patients about their average symptoms over the preceding two weeks [78], suggesting that these acute symptoms may contribute to chronic GI problems. Given the strong relationship between GI symptoms and quality of life, future work should examine ways to minimize GI symptom development during HD treatment.

The possibility that eating during HD treatment may exacerbate GI symptoms is frequently used as an argument against allowing patients to eat during HD treatment [19-21]. In the current study, we found no difference in GI symptoms among patients who ate versus those who did not eat during treatment. However, when we looked at the relationship between the intake of nutrients and GI symptom severity, we found both fat and fiber intake during treatment to be associated with greater indigestion. These relationships did not remain significant after the exclusion of outliers suggesting that the intake of large amounts of these nutrients may be undesirable. While the relationship between fiber and indigestion is well documented [84], the relationship between fat intake and these symptoms is more surprising. However, in hemodynamically unstable patients lipids are thought to disproportionately contribute to the postprandial development of intestinal ischemia [85]. Therefore, the safety of lipid intake during HD treatment is a topic that warrants future research.

In conclusion, the modified version of the GSRS appears to be a reliable tool for the measurement of GI symptoms associated with a single HD treatment. The development of GI

symptoms during a single treatment is considerably higher than previously reported and may be exacerbated by the intake of large amounts of certain nutrients such as fiber and fat. Future research should examine strategies for reducing GI symptoms associated with HD treatment to improve patient quality of life.

CHAPTER 5

INTRADIALYTIC PROTEIN SUPPLEMENTATION DOES NOT REDUCE BLOOD PRESSURE, TREATMENT EFFICIENCY, OR INCREASE GASTROINTESTINAL SYMPTOMS IN MAINTENANCE HEMODIALYSIS PATIENTS

Introduction

Providing nutrition during hemodialysis treatment has been shown to have numerous benefits including the prevention of muscle catabolism [11], attenuation of treatment associated inflammation [9], and reductions in mortality [17, 18]. Despite these benefits, eating during hemodialysis treatment is frequently not allowed in clinics within the United States. A number of reasons have been proposed to restrict nutrition during HD treatment including intradialytic hypotension, increased GI symptoms, and a reduction in the efficiency with which treatment clears uremic solutes [19-21, 23].

An alternative to allowing patients to eat during treatment is to allow for the consumption of liquid nutritional supplements. There is a perception among many clinics that liquid supplements would cause smaller hemodynamic alterations and, therefore, may be more suitable for use during HD treatment (Benner et al, in review). While liquid supplements do cause a well-documented pressor response that helps to maintain BP [86], they are also associated with more rapid gastric emptying which may exacerbate both the magnitude and duration of a drop in BP [87]. However, the effect of liquid nutritional supplements on hemodynamic variables during hemodialysis treatment has not yet been studied. Therefore, the purpose of this study was to test the effects of a liquid protein supplement containing 30 grams of whey protein on hemodynamics, GI symptoms, and treatment efficiency. Given previous data showing a minimal

hemodynamic response to protein, we hypothesized that protein supplementation would not have a significant effect on blood pressure during a normal hemodialysis treatment.

Methods

As a part of a larger trial, maintenance HD patients were recruited from dialysis clinics in central Illinois. Patients who received HD thrice weekly, were 30-80 years old, willing to receive intervention, received nephrologists clearance, were not currently receiving any intradialytic nutrition or exercise intervention, did not have CHF or COPD, and were not allergic to milk proteins were enrolled. Nine HD patients met these inclusion criteria and expressed interest in participating in this study. One HD patient received a transplant before finishing all of the treatments and was dropped from the study leaving us with 8 HD patients who completed all treatments.

Nutritional Supplement

Participants enrolled in the study received in a random order either: 1) standard dialysis session with no intervention (HD), 2) standard hemodialysis with the consumption of 30 grams of whey (milk) protein (HD + Protein), 3) Exercise + Protein, or 4) Exercise. For simplification, we have excluded the results of the exercise and exercise + protein group for this pilot study. The nutritional supplement was composed of 30 grams of whey protein mixed with four ounces of water. Nutritional analysis determined the breakdown of amino acids in the serving provided to patients to be 3.09 grams of leucine, 1.68 grams valine, 1.80 grams isoleucine, and 2.66 grams lysine. The supplement was given to patients 30 minutes into their treatment and they were asked to consume as much as possible in the following 15 minutes. All eight participants consumed the

entire study beverage. Additionally, patients underwent each of the following measurements during each of their treatment sessions.

Hemodynamic variables

We measured brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) on the non-dialyzing arm every 15 minutes using an automated cuff built-in to the dialysis machine. Measurements were taken in duplicate. If either SBP or DBP differed by more than 5 mm Hg, an additional measurement was taken. SBP, DBP, and HR were reported as the average of these measurements.

Blood Draw

Blood was drawn from the arterial line of the dialyzer prior to the start, 1.5 hours into the treatment, and 30 seconds after the end of the HD treatment in an EDTA plasma tube (treatment time varied for each patient). Blood samples were centrifuged, aliquoted, and stored at -80°C until the time of analysis.

Treatment Efficiency

The reduction ratio of urea (n=5) and β 2-microglobulin (n=7) in the blood was determined in a subset of patients using the formula: $([Pre] - [Post])/[Pre] \times 100$. Concentrations of urea in the blood were determined by enzymatic assay (BioAssay Systems, Hayward, CA) and β 2-microglobulin using a commercially available ELISA kit (abcam, Cambridge, UK).

We also reported single pool Kt/V from online clearance measurements provided by the HD clinic. In short, this is an estimate of urea removal based on the average conductivity of

sodium, which has a similar molecular weight, throughout the treatment. Data from one patient was unavailable due to a computer failure, leaving data available for seven patients.

Insulin

Insulin concentrations were determined in a subset of patients (n=5) at each time point using a commercially available ELISA kit (Alpco, Salem, NH). In a few instances, duplicates fell off the bottom of our standard curve. In these instances we replaced those values with 0 for statistical analysis.

Gastrointestinal Symptoms

GI symptoms were measured using a single item 7-point Likert scale (1= No Symptoms to 7 = Very Severe Symptoms) that was modified from the Gastrointestinal Symptom Rating Scale to measure acute symptoms [88]. In short, questions asked patients about the degree to which they felt hunger pain, bloating, nausea, and cramps throughout each specific treatment. These questions were asked to patients immediately following the conclusion of each HD session.

Statistical Analysis

Data are presented as mean \pm standard deviation. Comparisons between treatment parameters, GI symptoms, efficiency variables and the lowest BP achieved between the two conditions were tested using a paired t-test. The number of symptomatic treatments between the two conditions was analyzed using a chi-square analysis. Finally, BP throughout the treatment was compared using nested regression (treatment nested within participant) in proc genmod

using SAS version 9.4 (Cary, NC). When interaction terms were non-significant main effects were considered. Significance was set at an alpha of 0.05.

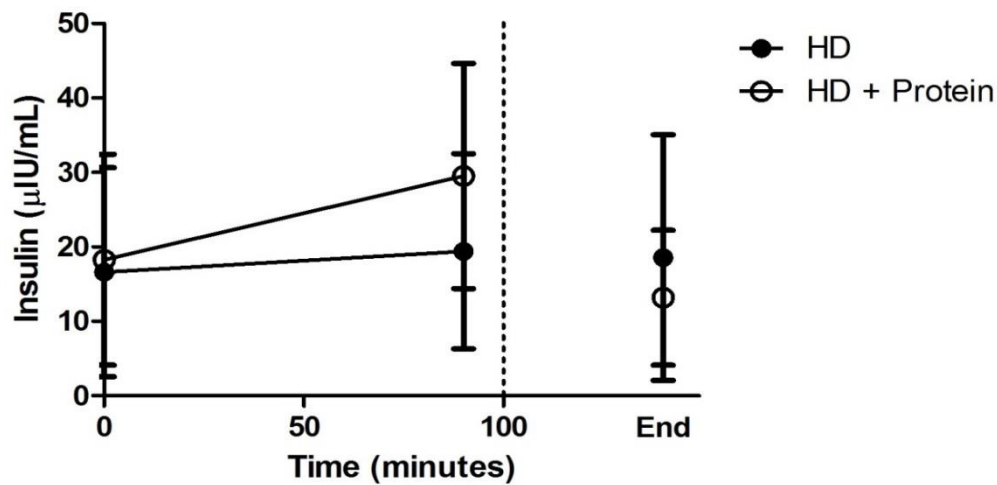
Results

Eight maintenance HD patients (4 males, 4 with diabetes, age 47 ± 13 years) were included in this pilot study. There were no differences in HD treatment on days where patients received HD or HD + Protein (Table 6). To determine the effect protein supplementation had on potentially vasoactive peptides, we ran plasma insulin on a subset of patients (n=5). Protein supplementation resulted in a numerical increase in insulin 1.5 hours into the treatment (Figure 2, 16.61 ± 14.03 to $19.41 \pm 13.1 \mu\text{IU/mL}$ in HD vs 18.28 ± 14.17 to $29.52 \pm 15.14 \mu\text{IU/mL}$ in HD + Protein) that was not statistically significant ($p=0.34$)

Table 6. Treatment parameters during standard hemodialysis with (HD + Protein) and without (HD) protein supplementation.

	HD	HD + Protein	P –value
Interdialytic Weight Gain (kg)	2.45 ± 1.79	3.19 ± 1.40	0.176
Treatment Time (minutes)	225.00 ± 16.04	223.13 ± 14.87	0.351
Ultrafiltration Volume (ml)	$3,162.9 \pm 1,479.0$	$3,265.0 \pm 1,308.3$	0.466
Relative Ultrafiltration (ml/kg/hr)	8.11 ± 3.38	8.46 ± 2.65	0.387
Dialysate Temperature (°C)	36.8 ± 0.4	$36.6 \pm 0.$	0.285
Blood Flow Rate (ml/min)	456.3 ± 41.7	450.0 ± 37.8	0.351
Dialysate Flow Rate (ml/min)	725 ± 88.6	700 ± 92.6	0.170

Figure 2. The effect of protein on plasma insulin concentration during hemodialysis treatment.

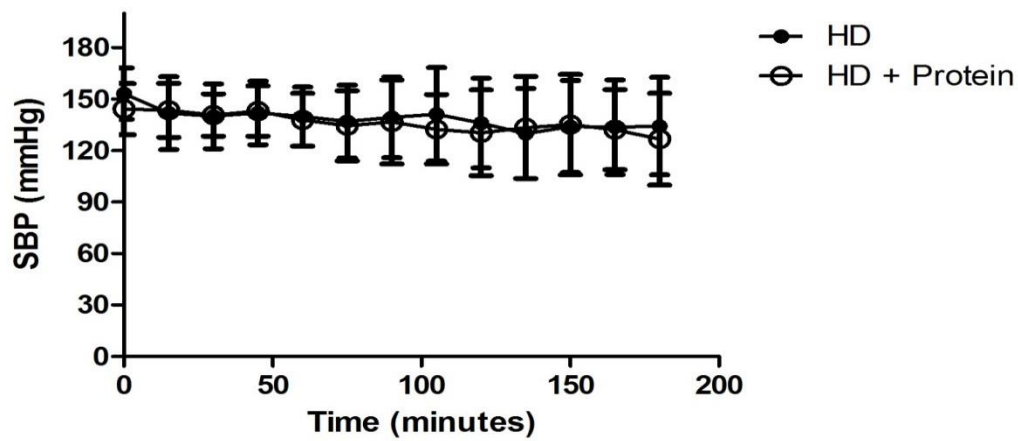


Plasma insulin concentrations during hemodialysis treatment with (HD + Protein) and without (HD) protein supplementation.

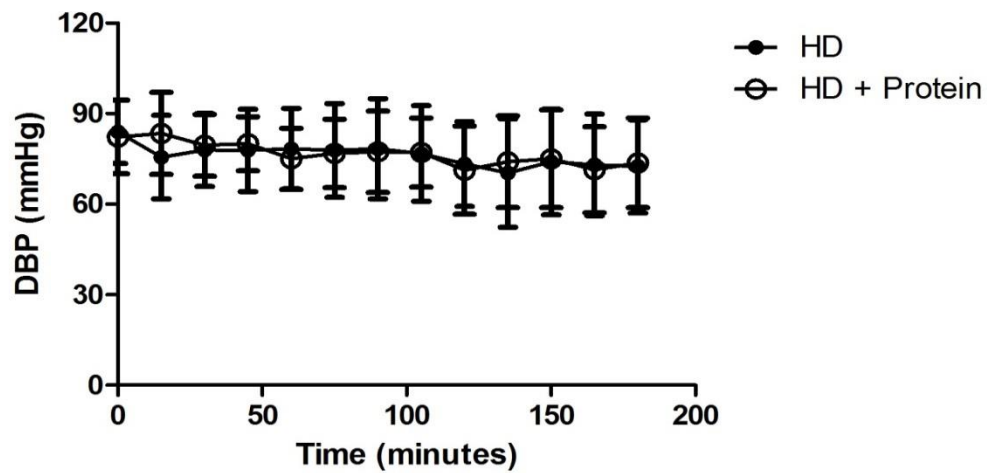
There was no difference between treatments in any hemodynamic parameter at the start of treatment, end of treatment, or the lowest BP achieved throughout the course of a treatment ($p > 0.05$ for all). Additionally, there was no interaction between the two treatment in any hemodynamic parameter (SBP, DBP, MAP, and HR, $p > 0.05$). However, SBP (Figure 3a, $p = 0.047$), but not MAP (Figure 3c, $p = 0.087$) or DBP (Figure 3b, $p = 0.19$) was reduced over the course of a HD treatment. Similarly, there was a significant decrease in HR over the course of the treatment ($z = 2.65$, $p = 0.008$).

Figure 3. Blood pressure changes during hemodialysis treatment with and without protein supplementation.

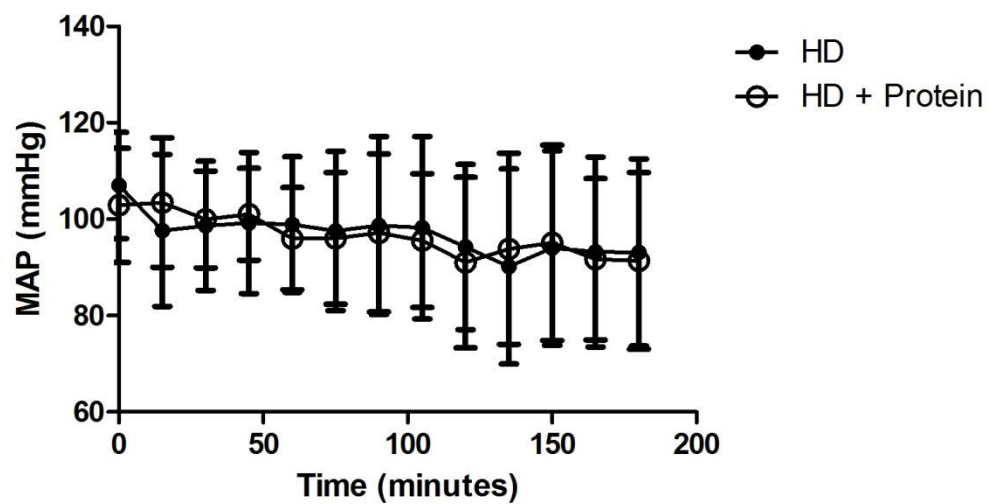
a.



b.



c.



Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) during hemodialysis treatments with (HD + Protein) and without (HD) protein supplementation.

We also examined the efficiency of solute removal (urea and β 2-microglobulin) in sessions with and without protein supplementation (Table 7). There was no difference in the efficiency with which treatments removed either urea (52.5% in HD vs 55.1% in HD + Protein, $p=0.707$) or β 2-microglobulin (33.4% in HD vs 28.8% in HD + Protein, $p=0.671$). Finally, there were no differences among the treatments in any measure of symptoms (Table 8).

Table 7. Efficiency of solute removal during HD treatment with and without protein supplementation.

	HD	HD + Protein	P – Value
Urea (n=5)			
Pre (mg/dl)	113.99 \pm 22.95	117.70 \pm 19.79	0.716
Post (mg/dl)	52.55 \pm 14.51	51.71 \pm 4.99	0.893
Reduction Ratio (%)	52.5 \pm 14.4	55.1 \pm 7.8	0.707
spKt/V (n=7)	1.42 \pm 0.33	1.35 \pm 0.29	0.243
β 2-Microglobulin (n=7)			
Pre (mg/l)	33.50 \pm 17.05	29.88 \pm 15.21	0.252
Post (mg/l)	21.03 \pm 10.07	22.70 \pm 20.36	0.787
Reduction Ratio (%)	33.4 \pm 26.3	28.8 \pm 26.9	0.671

Table 8. Gastrointestinal Symptoms during HD treatments with and without protein supplementation.

Symptom	HD	HD + Protein	p-value
Nausea	1.4±1.1	2.0±1.7	.231
Hunger	4.0±2.3	3.1±2.2	.395
Bloating	1.0±0.0	1.4±1.1	.356
Cramping	2.6±2.7	2.1±2.0	.356
Symptomatic (#/Total Treatments)	2/8	2/8	-

Data are presented as normalized scores on a 7-point Likert scale (1 = None, 7 = Severe).

Discussion

In this pilot study we recruited eight maintenance HD patients and monitored hemodynamics, GI symptoms, and treatment efficiency during a single HD treatment with and without protein supplementation. While SBP and MAP were reduced over the course of a HD treatment, we found no difference in SBP, DBP, MAP, or HR on days with or without protein supplementation. In addition, solute removal (measured by the reduction ratio of β_2 microglobulin and urea) and GI symptoms did not differ between treatments. These findings suggest that intradialytic supplementation with 30 grams of whey protein did not lead to the symptoms commonly cited as a reason to restrict intradialytic nutrition.

Intradialytic hypotension is the most common adverse event during maintenance HD treatment; occurring in up to 40% of all treatments [39, 89]. A common fear among renal clinicians is that allowing patients to consume food or nutritional supplements during treatment may exacerbate this problem [20, 21]. Certainly, there is a strong rationale for these concerns as the process of digestion has been shown to cause a reduction in total peripheral resistance (TPR),

especially in the splanchnic bed, a location that is a major source of vasoconstriction during the hypovolemic challenge of HD [58]. In healthy people, the reduction in TPR following a meal is compensated by an increase in cardiac output (CO) [50]. However, certain populations such as those with autonomic dysfunction may not produce adequate cardiac compensation, resulting in a drop in BP [50]. Many factors may influence the extent of this response such as meal composition, size, temperature, and even time of day. In the present study, we did not observe an interaction in either BP or HR when we supplemented patients with whey protein alone. This is consistent with previous studies suggesting that protein alone causes minimal hemodynamic changes [90]. However, additional energy and macronutrients may improve both the palatability of supplements and further improve patient nutritional status. Therefore, future work should examine the effect of a mixed-macronutrient supplement on hemodynamic changes during HD treatment.

The postprandial increase in splanchnic blood flow has also been hypothesized to reduce the efficiency with which a single HD treatment can remove unwanted solutes [62]. This phenomenon has been observed in some studies examining urea removal [60, 62]. However, urea removal kinetics may be complicated by the generation of urea during the digestion of protein [63]. In addition, urea, which is a small freely mobile molecule, may not adequately reflect the removal of all substances during HD [91]. Therefore, we also measured removal of the medium-size molecule β 2-microglobulin. We found no difference in the removal of either of these molecules during the course of a HD treatment with protein supplementation. This is perhaps not surprising given the lack of hemodynamic changes that we found. It remains unknown if a more hemodynamically challenging supplement may reduce treatment efficiency when given during HD treatment.

Similarly to IDH, GI symptoms are a common complication of HD treatment, occurring in approximately 10-15% of all treatments [67]. The etiology of GI symptom development during HD is complex, but likely includes fluid shifts, low blood pressure, and intestinal ischemia. These may be exacerbated by the additional metabolic demands of digestion or a postprandial drop in blood pressure. However, many clinicians have now argued that the hyperemic response to eating may prevent intestinal ischemia, maintain barrier function, and improve outcomes in times of hemodynamic instability [92, 93]. In the current study, we found no difference in the severity or prevalence of GI symptoms between HD treatment with and without protein supplementation. Given the etiology, it is possible that we did not see any difference in symptoms because we did not witness a difference in hemodynamics. Lipids have been implicated in causing greater metabolic demand in times of hemodynamic instability [85], and it remains unknown if the addition of lipid to our supplement may have caused GI distress.

There are a number of limitations to the current trial. First, we included only eight participants in this pilot study. While it may be argued that the current study is underpowered to detect differences in the main outcomes, the effect sizes of protein supplementation are almost zero. Therefore, we feel it is reasonable to conclude that protein supplementation did not influence any of the outcomes measured in the current trial. Another limitation is that we used only single item Likert scales to determine the difference in symptoms between HD and HD + Protein. While these single items can be unreliable, this data provides a good starting point for future trials. Finally, our current trial lacks mechanistic data on hemodynamic changes following protein supplementation. Despite not having data on peripheral resistance, it seems reasonable to conclude that any change in TPR was minimal given the lack of changes in BP or heart rate, a key determinant of cardiac output. Despite these limitations, this is the first study to examine the

influence of a liquid nutritional supplement consumed during HD treatment on hemodynamics, efficiency, and GI symptoms associated with the treatment.

In conclusion, we did not observe any effect of 30 grams of whey protein supplementation during HD treatment on hemodynamics, treatment efficiency, or GI symptoms. These data suggest that whey protein consumed during HD treatment does not increase the prevalence or severity of three of the main reasons cited to restrict oral nutrition during HD treatment. It remains unknown what the effect of carbohydrates, lipid, or additional energy may be on the postprandial response during HD treatment. However, given our data intradialytic protein supplementation may be a feasible way to improve nutritional status in maintenance HD patients who can tolerate it.

CHAPTER 6

THE ACUTE EFFECTS OF MIXED MACRONUTRIENT SUPPLEMENTATION DURING HEMODIALYSIS ON HEMODYNAMICS, TREATMENT EFFICIENCY, AND GASTROINTESTINAL SYMPTOMS

Introduction

Poor nutritional status is common and among the strongest predictors of mortality in patients undergoing HD treatment [4-6, 34]. Reduced dietary intake, especially on treatment days [8], is one factor that contributes to this poor nutritional status [29]. Providing food or nutritional supplements during maintenance HD has been shown to help restore intake, improve nutritional status, and reduce mortality in malnourished patients [17, 18]. However, many clinics do not allow patients to eat during treatment, primarily due to concerns related to hemodynamics, gastrointestinal (GI) symptoms, and treatment efficiency [21].

Despite clinician concerns, there are very few studies examining the safety of intradialytic nutrition [20]. A small number of trials have found that mixed-macronutrient solid meals may result in a transient reduction in blood pressure (BP) (Reviewed in [20]). Therefore, a number of clinics have encouraged liquid supplements as opposed to solid food (Benner et al., In review). We previously tested the effects of a liquid protein supplement given during treatment and did not find any differences in hemodynamics (Chapter 5). However, simple carbohydrates and lipids have been shown to cause greater hemodynamic alterations [90]. Therefore, the purpose of this study is to determine the effect of a mixed-macronutrient liquid nutritional supplement on treatment hemodynamics, GI symptoms, and treatment efficiency. We hypothesized that this mixed-macronutrient supplement would cause a transient drop in brachial

blood pressure, but that the hemodynamic alteration would not be large enough to be associated with greater symptoms or reductions in treatment efficiency.

Methods

Participants

We recruited 23 HD patients dialyzing at HD clinics located in central Illinois. Twelve of these patients met the inclusion criteria and agreed to participate. One female patient was dropped due to a medical issue that occurred after screening. This left us with eleven patients who completed the entire study protocol. Inclusion/exclusion criteria for participants included the following: 1) receiving thrice weekly HD; 2) received medical clearance from a Nephrologist at their dialysis clinic; 3) been on HD treatment for > 3 months due to physiological changes that typically occur at the onset of dialysis; 4) not have had hypotension requiring medical intervention during treatment more than four times or a hospitalization due to hypotension in the preceding two weeks, 5) not have a soy or milk protein allergy, and 6) not have a previous diagnosis of heart failure (an exclusion for physical performance testing). All patients provided informed consent and the trial was registered at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02371018) NCT02371018.

Baseline Testing

To attempt to control for fluid volume, all patients reported to the lab 18-24 hours following the end of their previous dialysis session for baseline testing. During this session patients underwent the following testing in the order described.

Anthropometric measurements

Standing height (Seca Stadiometer, Chino, CA) was determined to the nearest 0.1cm and weight to the nearest 0.1 kg (Tanita Corporation, Arlington Heights, IL) in duplicate with the participant in minimal clothing.

Body composition and bone density

Whole body fat, lean, and bone mass was measured by dual emission x-ray absorptiometry (DXA) (Hologic QDR 4500A, Bedford, Massachusetts). DXA scans were analyzed by an experienced technician blinded to the results of the acute testing sessions.

Autonomic function

Beat-to-beat heart rate (HR) was recorded in the supine position using a modified CM5 ECG configuration (Biopac Systems, CA) at a sampling rate of 1,000 Hz. Simultaneous beat-to-beat peripheral BP was derived via finger plethysmography (Finometer, FMS, the Netherlands). Breathing frequency was maintained in all participants at a rate of 12 breaths/min (0.2 Hz) with the aid of a metronome. Time and frequency domains were analyzed using WinCPRS software (Absolute Aliens, Finland).

Following this baseline test, patients underwent an orthostatic challenge with free breathing as previously described [94]. In short, following a minute of quiet rest, patients were asked to come to a standing position and remain standing for 5 minutes. The blood pressure response during the early (immediate) and prolonged (2 minutes) standing phase as well as the ratio of the minimum and maximum heart rate obtained in the first thirty seconds (30:15 ratio) were used to screen for autonomic dysfunction as previously described [94]. Results of the

orthostatic challenge were used only as a screening tool, and the number of abnormal responses was recorded. In three patients, we were unable to obtain reliable finger waveforms and their data was excluded.

Brachial blood pressure

Following a 10 minute rest, blood pressure was measured in duplicate using an automated cuff (Omron IntelliSense HEM-907XL, Lake Forest, IL). If blood pressure differed by >5mmHg additional measures were taken following a one minute rest. Once two measurements were obtained, they were averaged in all subsequent analyses.

Central blood pressure and wave reflection

Aortic blood pressure and central wave reflection were determined by tonometry using transformed peripheral blood pressure wave forms (measured at the radial artery) and a transfer function (SphygmoCor, AtCor Medical, Sydney, Australia) [95].

Arterial stiffness and structure

Aortic and femoral PWV were determined by tonometry (SphygmoCor, AtCor Medical, Sydney, Australia). In short, Aortic PWV was calculated as the time delay (Δt) between the R-wave of the ECG and the foot of the forward pressure wave form (Intersecting Tangent) between the carotid and femoral arteries [95, 96]. The distance for the aortic PWV measurement was determined by subtracting the distance between the sternal notch and the location of the carotid pressure measurement from the distance between the sternal notch and the location of the

femoral pressure (distance between the femoral measurement and dorsalis pedis measurement for femoral PWV).

Additionally, arterial ultrasound (Aloka, Japan) was used to determine arterial structure and function. Common carotid Intima Media Thickness (IMT) was determined from a segment 10mm proximal to the carotid bifurcation as previously described [97]. β -stiffness index was determined in the common carotid artery using a combination of B- and M-mode. Carotid blood pressure obtained from tonometry was used for pressure.

Cardiac ultrasound

Cardiac dimensions and function were determined by high resolution ultrasound (Aloka, Japan) according to the recommendations of the American Society of Echocardiography [98]. In short, images were obtained in the parasternal long-axis and four-chamber views. The parasternal long-axis view was used to determine left ventricular mass and volume from the Teichholz equation [99]. Left ventricular mass was indexed to height^{2.7} as described by de Simone [100]. Left ventricular volumes were indexed to body surface area. In the four chamber view, early and late flow in to the ventricular chamber (E and A) and tissue movement (E') were measured by Doppler. We were unable to obtain quality images in two participants in the long axis view and their data was excluded for cardiac dimension analysis.

Gait speed and shuttle walk test

We measured the normal walking speed of each patient over a 10 meter course in triplicate. Following gait speed, each subject underwent an incremental shuttle walk test designed to assess aerobic fitness in clinical populations as previously described [9]. The

participants were asked to navigate a 10m course with progressively increasing speeds until they were unable to reach the end of the course in the allocated time. One patient did not qualify for the shuttle walk test due to a previous diagnosis of heart failure and they were excluded.

Blood panel

Blood collected at the dialysis clinic during normally scheduled monthly blood draws was assessed for standard clinical lab parameters (plasma albumin, phosphorus, calcium, etc.) by Spectra Laboratories, a renal specific laboratory service provider (Rockleigh, NJ).

Intervention testing

Starting one week following baseline testing, participants were assigned to receive each of the following treatments in a random order: 1) standard hemodialysis (HD); or 2) standard hemodialysis with the consumption of a nutrition supplement (HD + ONS). During these interventions participants underwent tests falling into the following categories as described below: 1) dietary recalls, 2) hemodynamic response, 3) gastrointestinal symptoms, 4) blood collection, and 5) dialysate collection. The HD and HD + ONS testing took place during HD sessions on the same day of the week. Due to the potential differences caused by the prolonged break between treatments over the weekend, testing was not performed on participants first treatment of the week.

Nutritional intervention

During the session with nutrition supplementation patients received the renal specific nutritional supplement Nepro with Carb Steady (Abbott Nutrition, Columbus, Ohio). Patients

were asked to consume an 8 fl oz can of Nepro starting 30 minutes after the start of each session. To help control for gastric distension, the Nepro was split into two 4oz servings. The 4oz servings were each consumed over a 15 minute period so that the entire beverage was consumed by one hour into the treatment.

Diet recalls

Patients were asked to maintain diet consistency in the 48 hours leading up to each testing session. Diet recalls were collected by a Registered Dietitian over the 48 hours leading up to each treatment (dialysis and non-dialysis day) using the USDA 5-pass method. Because the time since a patient last ate can influence the hemodynamic response to eating, we asked for the time each food item was consumed. From this temporal information, the time since a patient last ate was calculated. Nutrient analysis on diet recalls was performed on Nutritionist Pro software (Axxya, Redmond, WA).

Brachial and aortic blood pressure

We measured brachial blood pressure and brachial wave forms to estimate aortic and central augmented pressure (AP) every half hour (Mobil-O-Graph, Stolberg, Germany) [101].

Beat-to-beat hemodynamic monitoring:

Beat-to-beat BP, ECG, and thoracic bio-impedance were used to determine the hemodynamic response to beverage consumption. In short SBP and DBP were determined from beat-to-beat finger plethysmography (Task Force Monitor CN Systems, Graz, Austria).

Transthoracic bioimpedance was used to estimate stroke volume during each beat and cardiac

output was reported as the product of stroke volume and heart rate from the ECG. Total peripheral resistance (TPR) was calculated from the quotient of mean arterial pressure (MAP) and cardiac output. Measurements are reported starting 15 minutes prior to the consumption of the beverage and followed for the next 150 minutes. Data are reported as the average of all beats in each 15 minute segment. Beats that were greater than 20% different from the previous beat were excluded under the assumption that this was a motion artifact.

The change in finger SBP, DBP, and MAP following administration of the beverage was calculated by subtracting the BP when the beverage was consumed (average of the 15 minutes preceding the start of supplementation) from the average of each 15 minutes segment (i.e. if the BP was lower than the starting BP the result would be a negative number). To determine the postprandial change in BP for correlation, the lowest SBP, DBP, and MAP achieved was subtracted from the respective value immediately prior to the administration of the supplement (30 minute).

Gastrointestinal symptoms:

Gastrointestinal symptoms throughout each treatment were monitored by a modified version of the gastrointestinal symptoms rating scale (GSRS) [81, 88]. The questionnaire has been modified to monitor acute ratings of GI symptoms during the HD treatment. Briefly, information on three of the domains (reflux, abdominal pain, and indigestion syndrome) was collected at the end of each treatment (HD or HD + ONS) session. Prior to the start of the next HD session (48-72 hours later), information on the other two domains (constipation, diarrhea) was collected for the time between treatments.

Blood and dialysate collection.

To measure dialysis efficiency and the change in plasma proteins we drew blood following European Task Force Recommendations with the help of clinic nursing staff [102]. Blood (5ml) was drawn from the dialysis line into a plasma tube containing EDTA after the dialysis patient was hooked up to the machine and before ultrafiltration began. In addition 5mL was drawn at 1.5 hours after the start of dialysis, 3 hours after the start, and 30 seconds after the end of ultrafiltration at a reduced flow rate [102]. Plasma was centrifuged, aliquoted, and stored at -80°C until analysis.

Treatment efficiency

Urea, calcium, and phosphorus were quantified in the blood using an autoanalyzer (Abaxis Piccolo Xpress, Union City, CA) [103]. β 2-microglobulin was determined by commercially available ELISA (Abcam, Cambridge, MA). Changes in urea, β 2-microglobulin, and phosphorus were measured by the ratio of removal (Equation 1) with the concentration of urea replaced by the concentration of the solute of interest.

Equation 1. $URR = (PreHD_{Urea} - PostHD_{urea})/PreHD_{Urea}$ [104]

Blood glucose

A small amount of blood (<0.5mL) was collected at 0, 30, 60, 90, 120, 180 and the end of each treatment from the arterial line. From these samples, blood glucose concentrations were determined in duplicate by the glucose oxidase method [105, 106].

Insulin

Insulin concentrations were determined in duplicate (n=7) from blood samples at 0, 90, and 180 minutes by a commercially available ELISA kit (Alpco, Salem, NH).

Treatment parameters

Dialysate composition, temperature, ultrafiltration rate and total volume, interdialytic weight gain, pre- and post-treatment weight, time on treatment, blood flow rate, dialysate flow rate, and other factors that may influence the outcomes of the intervention were collected for analysis. All patients were undergoing hemodialysis with high-flux polysulfone dialyzers (Fresenius).

Statistical Analysis:

Statistical analyses was performed using SAS statistical software version 9.3 (Cary, NC) with significance set at $p < 0.05$. Difference between dialysis treatment parameters, efficiency variables, pre-treatment BP, post-treatment BP, lowest BP, and gastrointestinal symptoms were compared by paired t-test. The number of treatments requiring medical intervention (administration of saline) was compared by a chi-square test. The association of treatment parameters, cardiac structure, and cardiac function with changes in BP was examined by Pearson correlation.

To compare how hemodynamic variables changed during treatments, repeated measures were modeled with treatment nested within subject in SAS using proc mixed. When interaction terms were non-significant main effects were considered. When the model indicated a significant interaction, differences between treatments were determined by LSD.

Results

Patient demographics and baseline testing

A description of the 11 participants who finished the study (Table 9) and their baseline arterial (Table 10), cardiac (Table 11), and autonomic function (Table 12) are presented in tables on the following pages.

Table 9. Participant characteristics.

Measure	Value
Age (y)	47 ± 13
Ethnicity (n, %)	
African American	7 (63.6)
Caucasian	3 (27.3)
Hispanic	1 (9.1)
Sex (n, %)	
Male	8 (72.7)
Female	3 (27.3)
Albumin (g/dl)	4.06 ± 0.35
Height (cm)	167.9 ± 6.7
Weight (kg)	94.3 ± 21.6
Waist:Hip	0.99 ± 0.11
Whole Body Percent Fat (%)	32.4 ± 11.4
Bone Mineral Density (g/cm)	1.18 ± 0.10

Table 10. Measures of arterial structure and function.

Measure	Value
Brachial SBP (mmHg)	144.1 \pm 16.5
Brachial DBP (mmHg)	79.2 \pm 11.8
Aortic SBP (mmHg)	128.4 \pm 14.6
Aortic DBP (mmHg)	80.8 \pm 12.0
Aortic Pulse Pressure (mmHg)	47.5 \pm 11.5
Heart Rate (bpm)	76.5 \pm 6.3
Augmented Pressure (mmHg)	10.4 \pm 7.2
Augmentation Index @ 75bpm (%)	21.1 \pm 10.9
Aortic Pulse Wave Velocity (m/s)	9.0 \pm 1.1
Femoral Pulse Wave Velocity (m/s)	9.6 \pm 1.8
β -Stiffness Index (AU)	8.2 \pm 4.5
Carotid IMT (mm)	0.62 \pm 0.13

SBP = systolic blood pressure, DBP = diastolic blood pressure, bpm = beats per minute, IMT = intima media thickness

Table 11. Measures of cardiac structure and function.

Measure	Value
Left Ventricular Mass ($\text{g/m}^{2.7}$)	84.11 ± 18.59
Hypertrophy (n, %)	(9,100)
Left Atrial Volume (ml)	41.55 ± 12.86
Normally Dilated (22-58)	9
Mildly Dilated (59-68)	1
Moderately Dilated (69-78)	1
Severely Dilated (>79)	0
End Diastolic Volume Index (ml/m^2)	65.87 ± 17.73
End Systolic Volume Index (ml/m^2)	26.87 ± 14.39
Stroke Volume Index (ml/m^2)	39.40 ± 12.33
Cardiac Output Index (l/min/m^2)	2.92 ± 0.83
Ejection Fraction (%)	61.13 ± 15.59
≥ 55 (n)	6
40-54.9	2
<40	1
E/A	1.21 ± 0.48
E/E'	10.17 ± 4.88
A Duration (s)	0.136 ± 0.043
Deceleration Time (s)	0.194 ± 0.033
Left Ventricular Diastolic Dysfunction (%)	63.6%

Table 12. Baseline autonomic function in patients undergoing HD.

Measure	Value
R – R Interval (ms)	794.8 ± 68.0
pNN50 (%)	6.52 ± 10.06
Ln Total Power	5.97 ± 1.89
Ln Low Frequency	4.54 ± 2.23
Low Frequency (nu)	54.2 ± 18.3
Ln High Frequency	4.30 ± 2.34
High Frequency (nu)	42.6 ± 17.9
LF/HF	1.80 ± 1.48
30:15 Ratio	1.13 ± 0.09
BRS Up (ms/mmHg)	7.01 ± 5.42
BRS Down (ms/mmHg)	9.30 ± 7.08

BRS = baroreceptor sensitivity, LF = Low frequency, HF = High frequency

Conditions associated with each treatment

In order to monitor how well patients adhered to our request to maintain diet, we monitored dietary intake over the 48 hours preceding each test. We found no difference in the time since a patient had eaten or in the intake of any nutrients between the two groups (Table 13). Additionally, we found no difference in any hemodynamically relevant parameters associated with each treatment (Table 14).

Table 13. Difference in average dietary intake over the 48 hours prior to HD or HD + ONS trials.

	HD	HD + ONS	p – value
Time since last meal (minutes)	473.8 ± 240.8	491.8 ± 282.0	0.366
Energy (kcal)	1811.66 ± 574.97	2055.48 ± 477.09	0.185
Protein (g)	69.46 ± 33.30	83.76 ± 29.74	0.063
Carbohydrate (g)	223.54 ± 78.87	255.59 ± 84.69	0.295
Fat (g)	65.26 ± 27.80	78.62 ± 18.33	0.203
Sodium (mg)	2768.78 ± 1292.67	3455.94±1033.13	0.091

Table 14. Treatment parameters for HD and HD + ONS trials.

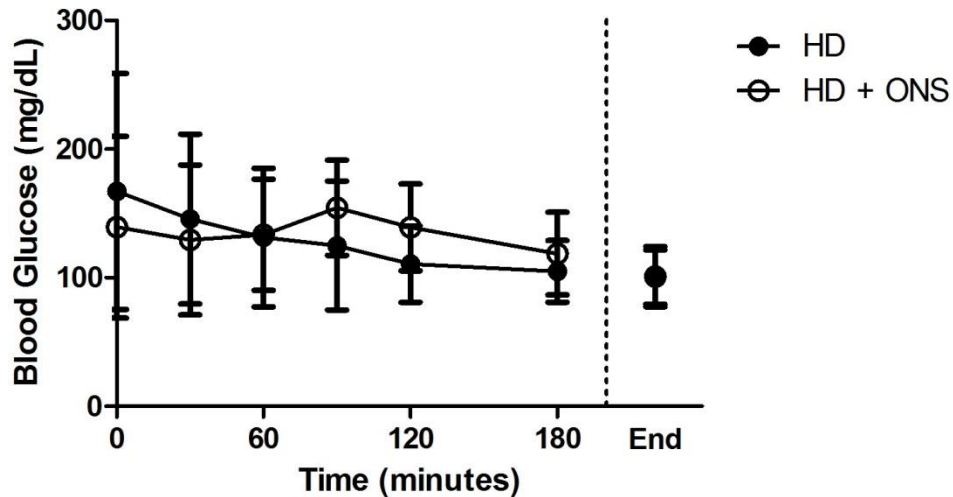
	HD	HD + ONS	P - value
Interdialytic Weight Gain (kg)	2.25 ± 0.82	2.48 ± 0.90	0.410
Start Weight (kg)	96.66 ± 22.11	96.70 ± 22.03	0.910
End Weight (kg)	93.48 ± 22.01	93.72 ± 21.68	0.264
Ultrafiltration (ml)	2924.55 ± 1056.71	3061.00 ± 634.52	0.689
Relative UF rate (ml/kg/min)	8.29 ± 3.01	8.77 ± 2.15	0.602
Blood Flow Rate (ml/min)	454.55 ± 35.03	454.55 ± 35.03	1.00
Dialysate Flow Rate (ml/min)	709.09 ± 70.06	681.82 ± 75.08	0.277
Saline (n)	2	2	1.00

Changes in vasoactive substances

To determine the influence of HD and HD + ONS on potentially vasoactive substances in the blood, we measured blood glucose and insulin throughout the treatment. There was a trend for an increase in blood glucose in HD + ONS (Figure 4a, $F_{1,20} = 3.94$, $p = 0.061$). Similarly, there was a numerical increase in postprandial insulin (Figure 4b) in the HD + ONS group, but this was not significant ($F_{1,12} = 0.38$, $p = 0.550$).

Figure 4. Changes in vasoactive substances during a standard hemodialysis treatment with and without an oral nutrition supplement.

a.



b.

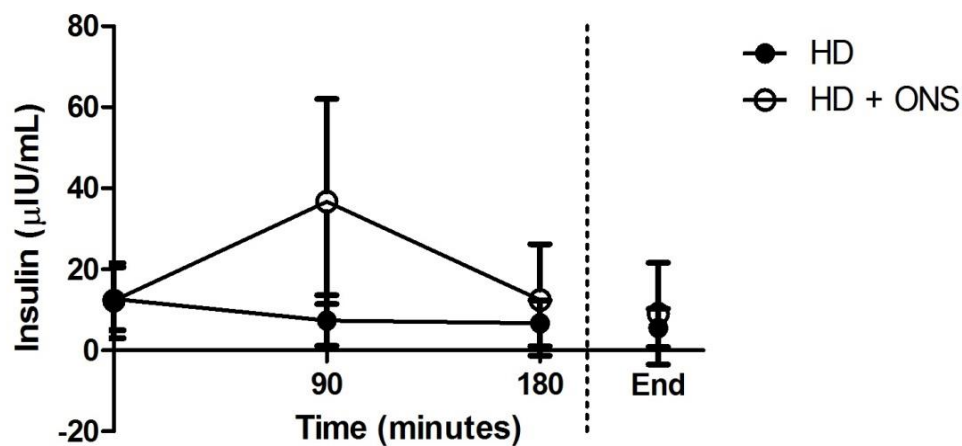


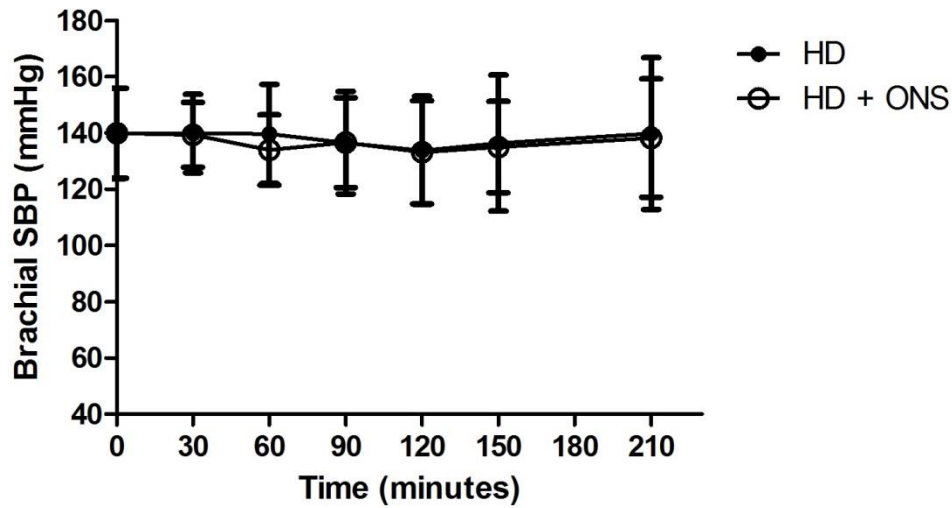
Figure 4. Changes in plasma glucose ($n = 11$) (a) and insulin ($n = 7$) (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment (HD + ONS). There was a trend for an increase in blood glucose in the HD + ONS ($p=0.06$), but no other interactions or main effects ($p > 0.05$).

Changes in brachial and aortic hemodynamics

To determine the effect of HD and HD + ONS on central hemodynamics we monitored brachial pulse wave forms intermittently throughout each treatment. We found no differences in any hemodynamic variables at the start of treatment on HD and HD + ONS day ($p > 0.05$). There was no change in brachial SBP (Figure 5a, $F_{1,18} = 0.03$, $p = 0.876$), brachial DBP (Figure 5b, $F_{1,18} = 0.83$, $p = 0.375$), aortic SBP (Figure 6a, $F_{1,18} = 0.11$, $p = 0.741$), aortic DBP (Figure 6b, $F_{1,18} = 1.17$, $p = 0.294$), AP ($F_{1,18} = 0.17$, $p = 0.681$), or systemic vascular resistance (Figure 7, $F_{1,18} = 1.03$, $p = 0.323$) between groups. Furthermore, when we compared the lowest BP achieved during the treatment, we found no difference in either brachial SBP (127.9 ± 20.51 mmHg in HD vs 121.6 ± 12.65 mmHg in HD + ONS, $p = 0.341$) or brachial DBP (76.5 ± 12.75 mmHg in HD vs 76.6 ± 12.88 mmHg in HD + ONS, $p = 0.977$).

Figure 5. Changes in brachial systolic blood pressure (SBP) and diastolic blood pressure during a standard hemodialysis treatment with and without an oral nutritional supplement.

a.



b.

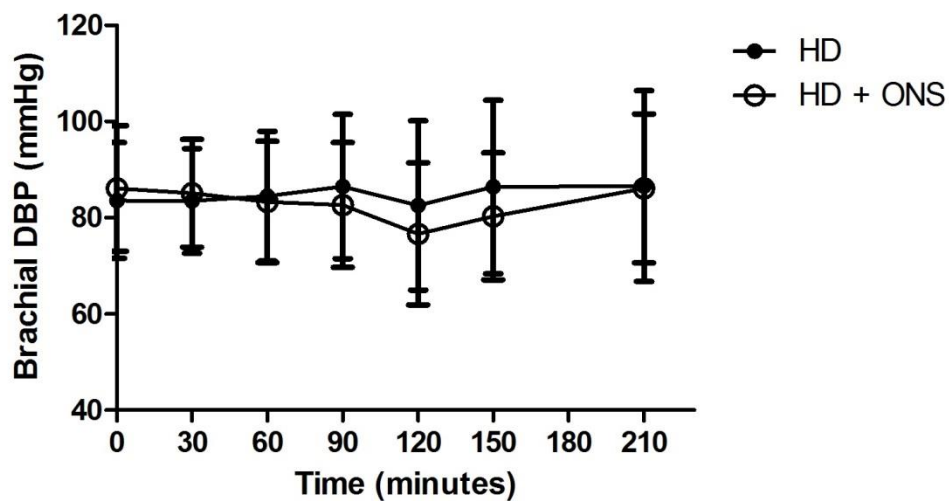
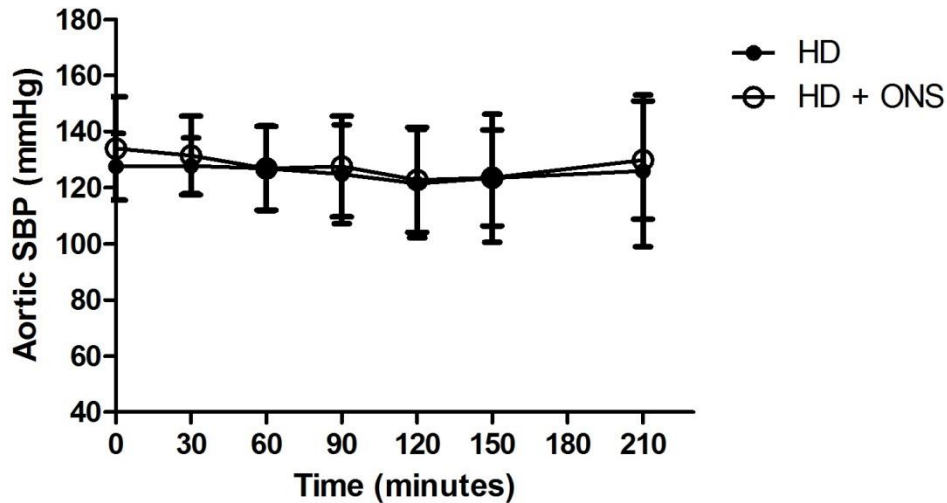


Figure 5. Changes in brachial systolic blood pressure (SBP) (a) and brachial diastolic blood pressure (DBP) (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment (HD + ONS). There were no interactions or main effects ($p > 0.05$).

Figure 6. Changes in aortic systolic blood pressure (SBP) and diastolic blood pressure during a standard hemodialysis treatment with and without an oral nutritional supplement.

a.



b.

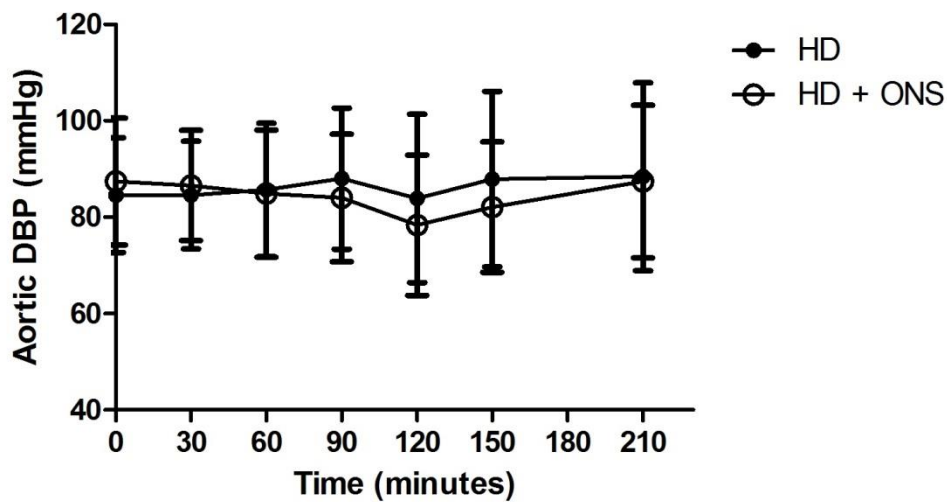


Figure 6. Changes in aortic systolic blood pressure (SBP) (a) and aortic diastolic blood pressure (DBP) (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment (HD + ONS). There were no interactions or main effects ($p > 0.05$).

Figure 7. Changes in systemic vascular resistance during HD treatment with and without ONS.

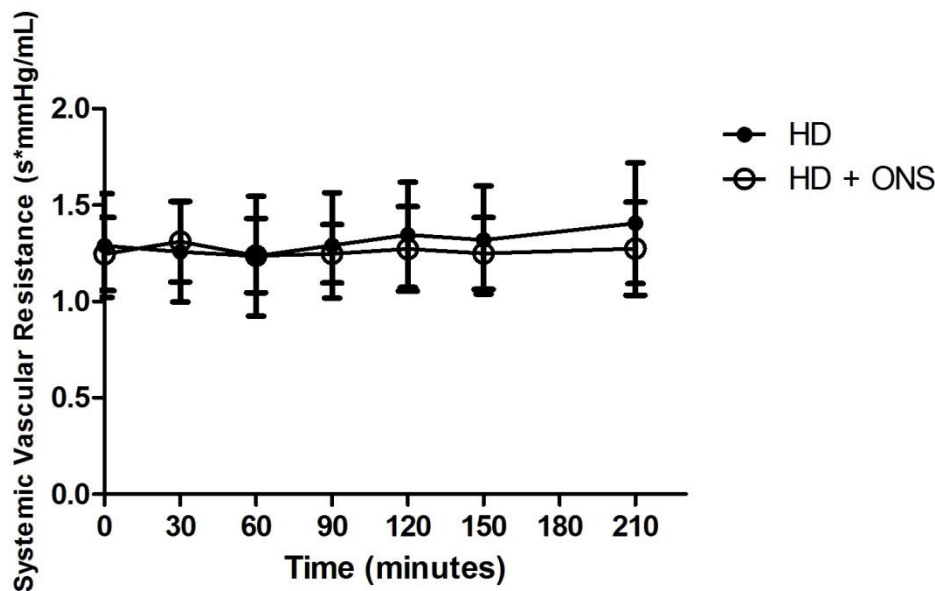


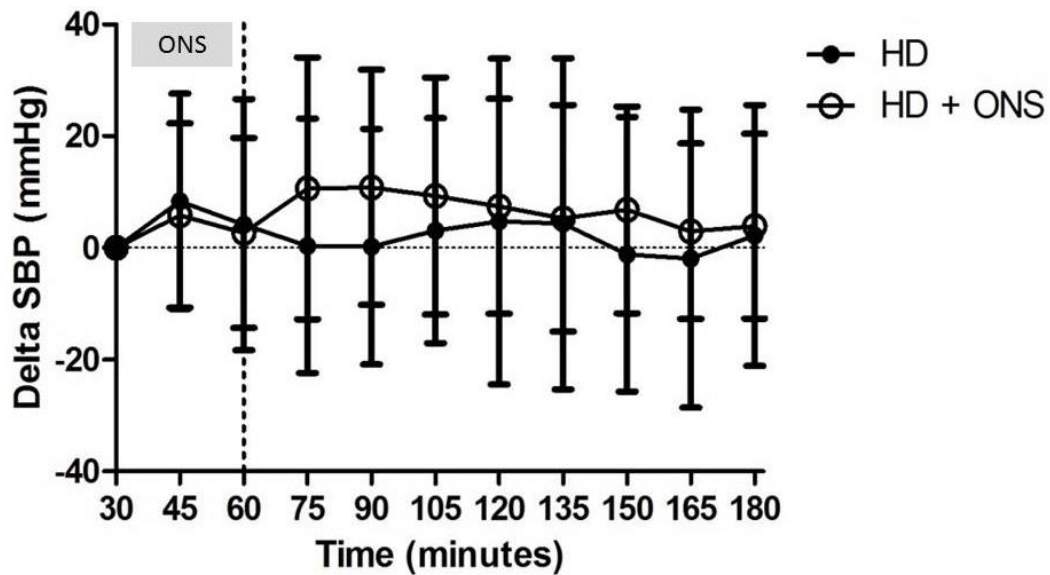
Figure 7. Changes in systemic vascular resistance during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment (HD + ONS). There were no interactions or main effects ($p > 0.05$).

Beat-to-beat postprandial hemodynamic changes

To determine the hemodynamic changes associated with the consumption of the study beverage, we monitored beat-to-beat hemodynamics for 150 minutes following the consumption of the study beverage. We found no difference in the change in SBP (Figure 8a, $F_{1,20} = 0.25$, $p = 0.621$), DBP (Figure 8b, $F_{1,20} = 0.02$, $p = 0.880$), TPR (Figure 9a, $F_{1,20} = 0.01$, $p = 0.914$), or CO (Figure 9b, $F_{1,20} = 0.19$, $p = 0.667$). However, a main effect did exist for CO ($F_{1,20} = 4.85$, $p = 0.040$) to be elevated following the ONS supplementation, primarily due to an increase in heart rate ($F_{1,20} = 4.38$, $p = 0.049$).

Figure 8. Postprandial change in beat-to-beat blood pressure with and without ONS during HD treatment.

a.



b.

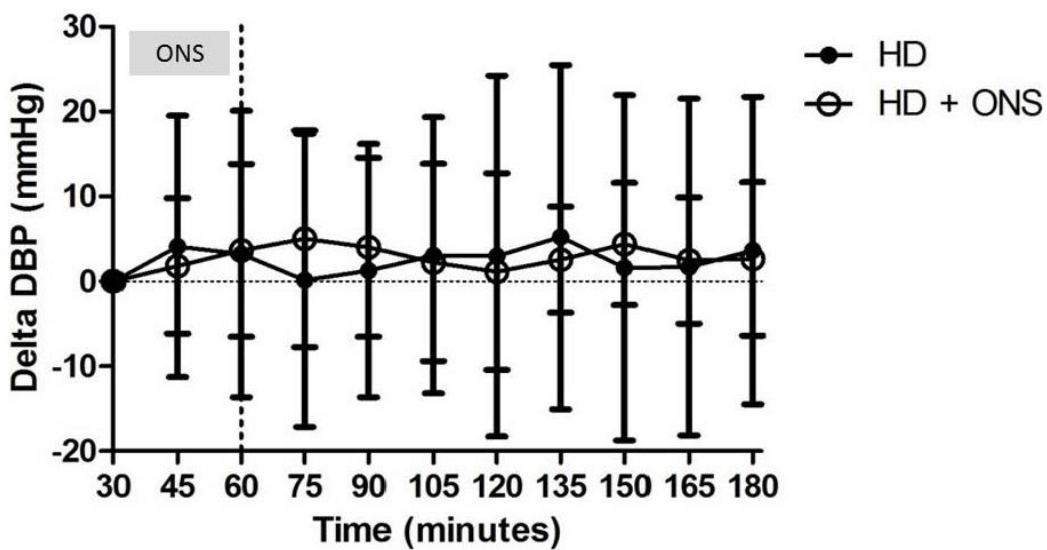
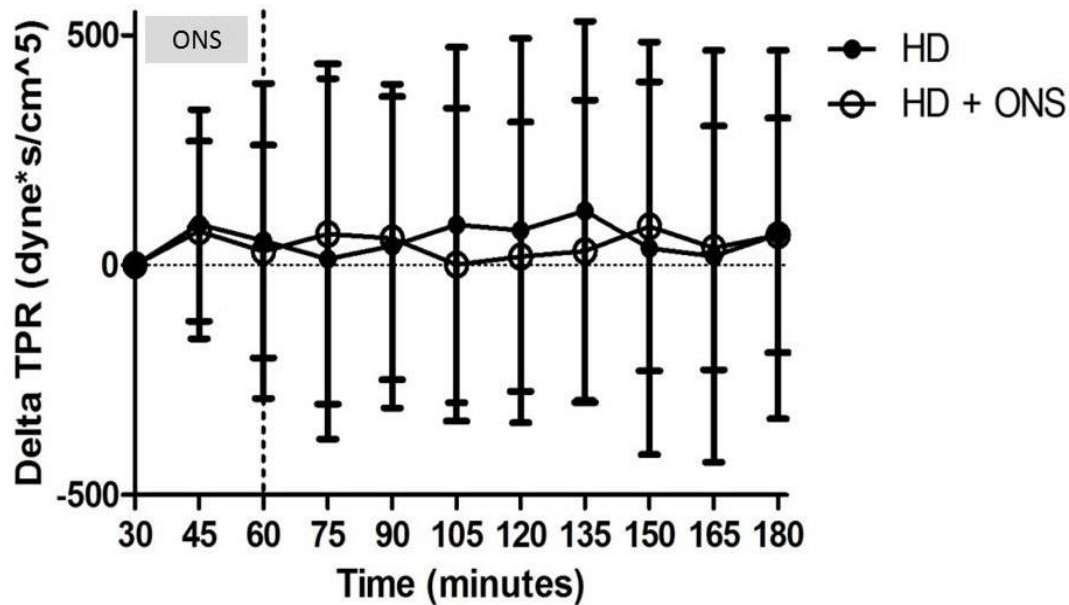


Figure 8. Changes in beat-to-beat systolic blood pressure (SBP) (a) and diastolic blood pressure (DBP) (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment. There were no interactions or main effects ($p > 0.05$).

Figure 9. Changes in total peripheral resistance and cardiac output with and without ONS during HD treatment.

a.



b.

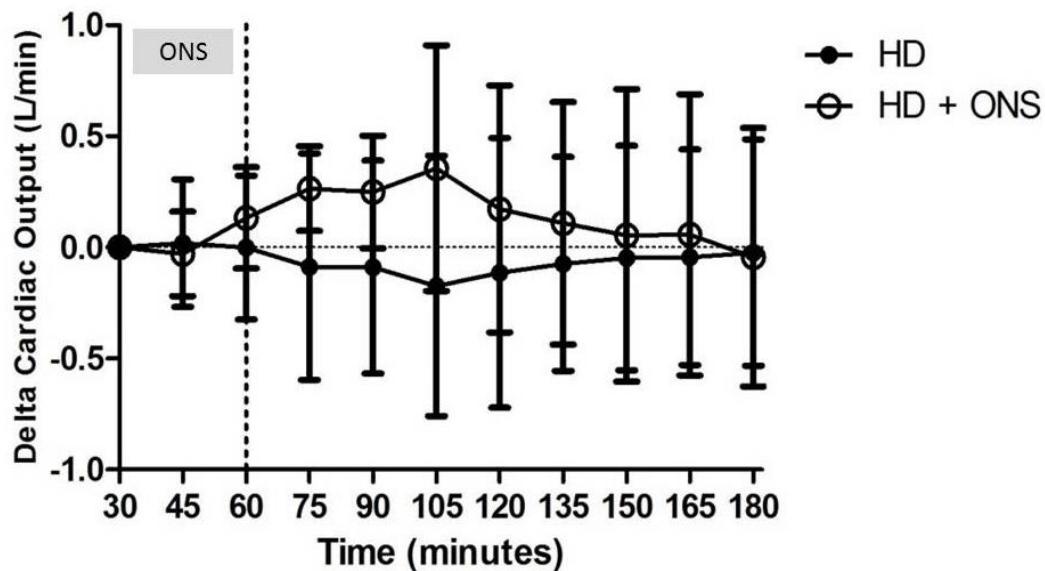
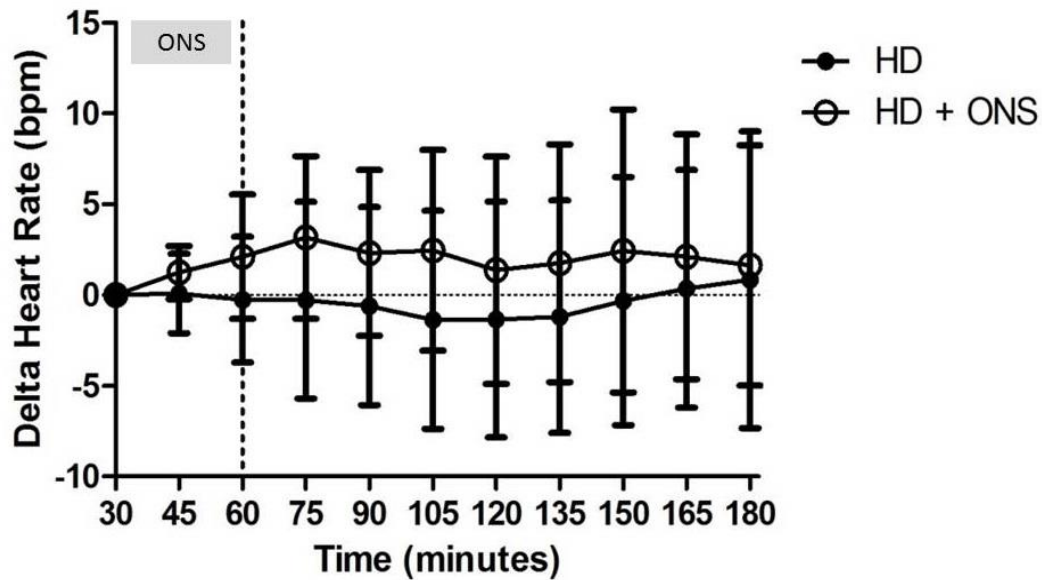


Figure 9. Changes in total peripheral resistance (a) and cardiac output (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment. There were no interactions ($p > 0.05$), but a significant main effect of treatment existed for the change in cardiac output ($p = 0.04$).

Figure 10. Postprandial change in heart rate and stroke volume during HD treatment with and without ONS.

a.



b.

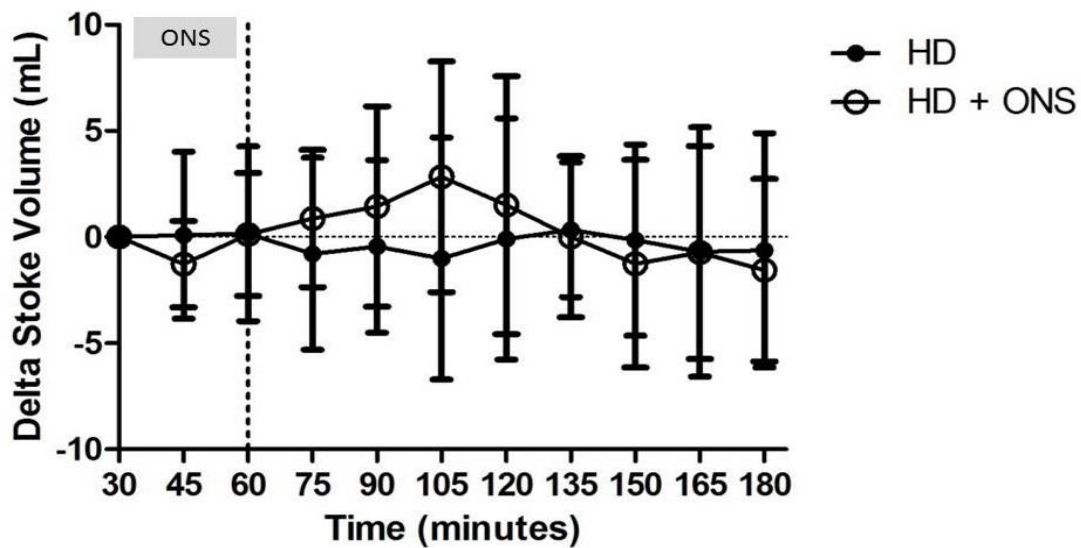


Figure 10. Changes in heart rate (a) and stroke volume (b) during a standard hemodialysis treatment (HD) and HD in which patients consumed a liquid mixed-macronutrient supplement 30 minutes into treatment. There were no interactions ($p > 0.05$), but a significant main effect of treatment existed for the change in heart rate ($p = 0.05$).

Solute removal

We measured the removal of a number of solutes over the course of a HD treatment with and without ONS. There was no difference in the reduction ratio of the medium-sized molecule β 2-microglobulin or in the final concentration (Table 15). We also found no difference in estimated urea removal (spKt/V) by online clearance ($p = 0.351$).

Table 15. No difference in solute removal during HD and HD + ONS.

Solute	Standard Hemodialysis	Nutrition Supplementation	P-Value
Single Pool Kt/V	1.73	1.65	0.351
β2-Microglobulin			
Pre (mg/l)	29.46 \pm 12.03	27.67 \pm 13.29	0.459
Post (mg/l)	14.88 \pm 7.28	16.08 \pm 6.56	0.505
Reduction Ratio (%)	48.97 \pm 18.62	37.89 \pm 15.63	0.250

Gastrointestinal symptoms

To determine the effect of ONS on GI symptom development associated with a single treatment, we administered a modified version of the GSRS following each treatment. There was no difference between the severity of GI symptoms in any domain between HD and HD + ONS (Table 16).

Table 16. No difference in standardized gastrointestinal scores for HD and HD + ONS trials.

Scale	Standard Hemodialysis	Nutrition Supplementation	P-Value
Abdominal Pain	1.36 ± 0.53	1.39 ± 0.57	0.878
Reflux Syndrome	1.09 ± 0.30	1.05 ± 0.15	0.676
Indigestion Syndrome	1.42 ± 0.70	1.27 ± 0.61	0.450
Diarrhea Syndrome	1.39 ± 0.55	1.70 ± 0.85	0.308
Constipation Syndrome	1.18 ± 0.17	1.48 ± 0.70	0.148

Relationship between descriptive variables and changes in BP

To determine the relationship between the changes in BP following ONS and underlying CV structure and function, we correlated select CV and treatment variables with the maximum change in BP following beverage consumption (Table 17). The only variable correlated with the change in BP was baroreceptor sensitivity.

Table 17. Associations between descriptive variables and the change in blood pressure following the consumption of the study beverage.

Variable	Delta SBP (mmHg)	Delta DBP (mmHg)	Delta MAP (mmHg)
Age (y)	-.193	-.073	-.274
Albumin (g/dl)	.389	.237	.422
Relative Ultrafiltration Rate (ml/kg/min)	-.122	-.428	-.242
Shuttle Walk Test	.224	.220	.318
Augmentation Index @ 75bpm (%)	-.447	-.379	-.451
Aortic PWV (m/s)	.266	-.436	-.059
IMT (mm)	-.251	-.421	-.440
LF/HF	-.163	-.337	-.237
BRS Up (ms/mmHg)	.439	.847*	.676
BRS Down (ms/mmHg)	.790*	.347	.706*
Ejection Fraction (%)	.087	-.455	-.196
Left Atrial Volume (ml)	.325	.089	.172

p < 0.05*

Discussion

In the current study, we compared hemodynamics, GI symptoms, and treatment efficiency during a standard HD treatment and a standard HD treatment in which patients consumed a mixed-macronutrient liquid supplement. After ONS, cardiac output and heart rate were significantly higher during HD + ONS, but there were no other significant hemodynamic changes. Despite the higher cardiac output, we saw no difference between HD or HD + ONS in any measure of GI symptoms or treatment efficiency. When we attempted to determine risk factors for a postprandial drop during HD treatment, only baseline BRS was correlated with the maximum drop in BP following the consumption of the study beverage.

Despite the benefits, many clinics within the United States do not allow patients to eat during HD treatment due to concerns about hemodynamic stability [19-21]. Previous trials on this topic have focused exclusively on solid, mixed-macronutrient meals and produced equivocal hemodynamic results [20]. However, many clinics have more lenient policies towards liquid nutritional supplements. Despite these more lenient policies these supplements have been sparsely evaluated. We previously found that a liquid supplement containing 30 grams of whey protein did not result in any significant hemodynamic alterations (Kistler et al., In prep (Chapter 5)). Given that simple carbohydrates appear to be the primary cause of postprandial reductions in BP, in this trial we tested the effects of a mixed-macronutrient supplement formulated specifically for HD patients. However, similar to our findings with whey protein, we found no reduction in any measure of BP.

The postprandial hemodynamic response is complicated and dependent on many factors including gastric emptying, cardiovascular function, and meal composition [107]. In patients who suffer a postprandial drop in BP there is generally an inadequate response to a drop in

systemic vascular resistance (SVR) brought about by a meal [50]. It may be hypothesized that this response may be exacerbated by the challenge of HD treatment, especially given that eating would reduce SVR in vascular beds that tend to constrict in response to hypovolemia [58]. In the current trial, we did not find a significant reduction in SVR in the HD + ONS compared to the HD treatment. One reason for the equivocal hemodynamic results in the current trial may be the modified maltodextrin added to this specific ONS supplement to slow intestinal absorption and reduce the postprandial spike in blood glucose [108]. This would minimize the early arrival of simple carbohydrates such as glucose which appear to be responsible for majority of the BP drop after eating [107]. However, a number of mechanistic questions remain unanswered including the effect of nutritional supplements on local environments, especially those that are prone to ischemic damage during HD treatment such as the heart, brain, and intestine.

Allowing patients to eat during HD treatment has also been hypothesized to contribute to the development of GI symptoms [21]. One way in which food may contribute to GI symptoms is through the potential postprandial reduction in BP [39]. Low BP during HD treatment has been linked to ischemic damage of many organ systems such as the heart and the brain [109]. The intestine is another organ prone to ischemic damage in kidney disease patients, especially those undergoing HD [79, 110]. In the present study, we measured aortic pressure and central augmented pressure which may better estimate the environment being experienced by central organs. One reason we may not have seen a change in any of the GI symptom domains is the lack in change in these pressures. Despite these data, providing nutrition in times of hemodynamic instability remains controversial due to the increased metabolic demand of the intestine and mucosal barrier at a time when perfusion is reduced [93, 111]. However, most studies appear to show that the increase in blood flow during digestion leads to improved

oxygenation, barrier function, and outcomes [85, 93, 111]. In the present study, we did not measure the local hyperemic response, however, the potential role intradialytic nutrition supplementation may play on gut health is an important target of future research.

An additional concern has been raised about the role digestion may have on the ability of HD to remove unwanted solutes. It has been hypothesized that increasing the amount of blood in the digestive tract may reduce the blood available to interact with the dialyzer [62]. Previous trials on eating during treatment have produced mixed results [60-62], although these studies may be confounded by the effects of protein digestion on urea kinetics [63]. Therefore, in the current trial we measured the removal of additional solutes less likely to be influenced by the process of digestion. When we looked at these additional markers, we found no difference in any measure of solute removal between treatments with and without ONS. These results coincide with those of our previous surveys, which found that this is not a problem frequently observed in clinical practice [21].

Finally, we hoped to identify the potential relationship between the change in BP following ONS and cardiovascular structure and function. Of the cardiovascular and treatment parameters we tested, only baseline baroreceptor sensitivity was significantly associated with the maximum drop in BP. This is consistent with previous studies that have associated reduced baroreceptor function with the postprandial drop in BP [50]. Impaired autonomic function is common in HD patients due to a variety of comorbidities that include diabetic and uremic neuropathy, hypotension, arterial stiffness, and issues with systemic nitric oxide [112]. Future studies should examine more thoroughly the relationship between autonomic function and postprandial blood pressure in HD patients.

In conclusion, we found that providing ONS during HD treatment did not reduce any measure of BP throughout the treatment. Although we did not find changes in BP, we did find a significant increase in CO and HR over the 150 minutes following supplementation. Despite these hemodynamic alterations we found no increase in GI symptoms or reduction in treatment efficiency. Similar to previous studies on postprandial hemodynamics, we found baroreceptor sensitivity to be related to the maximum drop in BP following the beverage. Future research should determine if patients with reduced autonomic function may be at increased risk of a postprandial drop in BP during HD treatment and the effect of nutrition supplementation on gut barrier function. However, the current trial does not support the practice of restricting nutrition during HD treatment.

CHAPTER 7

CONCLUSIONS

Maintenance HD is a catabolic condition associated with poor nutritional status.

Providing nutrition during HD improves nutritional status and outcomes. However, this practice is controversial due to concerns that include hemodynamic instability, GI distress, and reduced treatment efficiency. There is a lack of data on the proposed harms associated with eating during treatment, and this has led to clinic practices that differ drastically throughout organizations, regions, and the world.

Therefore, we set out to use a combination of survey and interventional research to provide clinicians with data on the relative frequency and severity of the proposed harms associated with eating during treatment. Our survey results indicated that with the exception of GI symptoms and hypotension, most of the concerns related to eating during treatment were not frequently observed in clinical practice. Furthermore, GI symptom severity was not greater in patients who ate during treatment versus those who did not eat during treatment. However, certain nutrients, specifically fiber and fat, may be associated with greater indigestion in large amounts.

When we performed randomized crossover trials using liquid supplements that contained protein or combinations of the three macronutrients, we found no difference in blood pressures throughout the treatment, symptoms associated with the treatment, or the removal of solutes by the treatment. However, we did find significantly higher cardiac output following a renal specific mixed-macronutrient supplement. The maximum drop in blood pressure following the consumption of the supplement was associated with baseline baroreceptor sensitivity, but no other aspect of cardiovascular structure or function. Although additional research is needed to help develop guidelines, these data do not seem to support the current practice in the United

States of restricting patients from eating during maintenance HD treatment. Future research should focus on identifying patients at risk of a postprandial drop in BP, the effects of nutrition supplementation on tissues prone to ischemic damage such as the heart and brain, and to further document the benefits of intradialytic nutrition, especially in patients who may not be classified as malnourished.

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APPENDIX

Acute gastrointestinal symptoms questionnaire (Day 1)

To be given immediately following HD treatment

The following questions ask about whether you experienced stomach or intestinal discomfort during your dialysis treatment. Please circle your response for each question.

1. Were you bothered by stomach pain during the treatment that just ended?

(Stomach pain refers to all kinds of aches or pains in your stomach or belly)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

2. Were you bothered by heartburn during the treatment that just ended?

(Heartburn refers to the burning pain or discomfort behind the breastbone in your chest)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

3. Were you bothered by acid reflux during the treatment that just ended? (Acid reflux refers to regurgitation or flow of sour or bitter fluid into your mouth)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

4. Were you bothered by nausea during the treatment that just ended? (Nausea refers to a feeling of wanting to be sick)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>

Discomfort

5. Were you bothered by hunger pains during the treatment that just ended?
(Hunger pains refers to the hollow feeling in the stomach is associated with the need to eat between meals)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

6. Were you bothered by rumbling in your stomach during the treatment that just ended? (Rumbling refers to the vibrations or noise in the stomach)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

7. Were you bothered by burping during the treatment that just ended? (Burping refers to bringing up air or gas through the mouth)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

8. Were you bothered by bloating during the treatment that just ended? (By bloating we mean swelling in the stomach)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

9. Were you bothered by gas or flatus during the treatment that just ended?
(Passing gas or flatus refers to the release of air or gas from the bowel)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

Modified from the Gastrointestinal Symptom Rating Scale American English Version (2/26/2014)

Acute gastrointestinal symptoms questionnaire (Day 2)

To be given 48-72 hours after the previous HD treatment

The following questions ask about whether you experienced stomach or intestinal discomfort after your previous dialysis treatment. Please circle your response for each question.

1. Have you been bothered by constipation since your previous hemodialysis treatment? (Constipation refers to a reduced ability to empty your bowels)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

2. Have you been bothered by diarrhea since your previous hemodialysis treatment? (Diarrhea refers to frequent loose or watery stools)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

3. Have you been bothered by loose stools since your previous hemodialysis treatment? (If your stools have been alternately hard and loose, this question only refers to the extent to which you have been bothered by your stools being loose)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

4. Have you been bothered by hard stools since your previous hemodialysis treatment? (If your stools have been alternately hard and loose, this question only refers to the extent to which you have been bothered by your stools being hard)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

5. Have you been bothered by an urgent need to have a bowel movement since your last hemodialysis treatment? (This urgent need to open your bowels makes you rush to the toilet).

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

6. When going to the toilet since your last hemodialysis treatment, have you had a feeling of not completely emptying your bowels? (The feeling that after a bowel movement, there is still more stool that needs to be passed)

1	2	3	4	5	6	7
<i>No</i>	<i>Slight</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately</i>	<i>Severe</i>	<i>Very Severe</i>
<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Discomfort</i>	<i>Severe</i>	<i>Discomfort</i>	<i>Discomfort</i>
				<i>Discomfort</i>		

Modified from the Gastrointestinal Symptom Rating Scale American English Version (2/26/2014)