
Effect of high amylose resistant starch (HAM-RS2) supplementation on biomarkers of inflammation and oxidative stress in hemodialysis patients: a randomized clinical trial

Hamid TAYEBI KHOSROSHAHI,¹ Nosratola D. VAZIRI,² Behzad ABEDI,³
Bahlol Habibi ASL,⁴ Morteza GHOJAZADEH,⁵ Wanghui JING,²
Amir Mansur VATANKHAH⁶

¹Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; ²Division of Nephrology and Hypertension, UC Irvine Medical Center, Irvine, California, USA; ³Department of Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran; ⁴Faculty of pharmacology, School of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran; ⁵Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran; ⁶Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Introduction: Systemic inflammation and oxidative stress play a central role in the pathogenesis of cardiovascular disease and numerous other complications of CKD. Recent studies demonstrated that consumption of a diet enriched with amylose (HAM-RS2), attenuates oxidative stress and inflammation, and improves intestinal microbiome in CKD rats. The present study was designed to explore the effect of dietary amylose supplementation in hemodialysis patients.

Methods: Forty-six stable hemodialysis patients were randomized to receive biscuits containing 20 g/day during the first four weeks and 25 g/day in the next four weeks of either HAM-RS2 or wheat-flour. Fasting predialysis blood samples obtained before, during and at the end of trial were processed for biomarkers of oxidative stress and inflammation.

Findings: There was no significant difference in baseline clinical or biochemical parameters between the two groups. Serum levels of TNF- α , IL-6, and malondialdehyde declined significantly ($P < 0.05$) in the HAM-RS2-treated group but remained unchanged in the placebo-treated group. No significant difference was observed in serum Interleukin-1 β (IL-1 β) and hs-CRP concentrations and total antioxidant activity between two groups. Serum urea and creatinine concentrations significantly declined and severity of constipation improved in HAM-RS2-treated patients ($P < 0.05$). HAM-RS2 consumption was well tolerated and did not cause discernible side effects.

Discussion: Administration of HAM-RS2 for eight weeks significantly reduced levels of inflammatory and oxidative markers in hemodialysis patients confirming the results observed in CKD

Correspondence to: N. D. Vaziri, MD, MACP, Division of Nephrology and Hypertension, C351, Medical Science C, School of Medicine, University of California, 101 The City Drive, Irvine, CA 92868, USA. E-mail: ndvaziri@uci.edu

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animals. Long term trials are needed to explore the impact of HAM-RS2 supplementation on clinical outcomes in end stage renal disease population.

Key words: End stage renal disease, hemodialysis, high maize resistant starch2, inflammatory marker, oxidative markers

INTRODUCTION

Chronic kidney disease (CKD) has emerged as a major cause of morbidity and mortality world-wide. CKD affects close to 16% of the adult population and consumes a disproportionate share of the health care resources in the developed countries.¹⁻³ Advanced CKD results in accelerated cardiovascular disease, cachexia, anemia, and numerous other complications which impair the quality of life and shorten the life span in this population. Systemic inflammation and oxidative stress are common consequences of CKD and play a central role in progression of kidney disease and the associated cardiovascular disease and many other complications.⁴⁻⁶ Oxidative stress is condition in which production of reactive oxygen species (ROS) exceeds the capacity of the antioxidant system and result in tissue damage and dysfunction by uncontained ROS. Oxidative stress in CKD is caused by a combination of increased ROS production and impaired antioxidant capacity.⁴⁻¹⁰ Impaired antioxidant capacity in CKD is due to the defective activation of the transcription factor, Nrf2, which is the master regulator of close to 250 genes encoding antioxidant and cytoprotective enzymes and proteins.¹¹

Oxidative stress and inflammation are inseparably linked as each triggers and amplifies the other. Emerging evidence points to the gastrointestinal tract as one of the major sources of systemic inflammation in patients and animals with CKD.^{12,13} In this context, several studies have demonstrated disruption of the gastro-intestinal epithelial barrier structure and function in CKD animals¹⁴⁻¹⁶ and profound changes in the composition and function of the intestinal microbiota in humans with end stage renal disease (ESRD) and in animals with advanced CKD.¹⁷ The CKD-induced microbial dysbiosis and disruption of the gut epithelial barrier contribute to systemic inflammation by: a- raising generation of microbial toxic and pro-inflammatory products and b- accommodating the entry of the noxious microbial byproducts and other harmful luminal contents into the intestinal wall and systemic circulation through disrupted epithelial barrier.¹⁸

The following factors have been shown to contribute to the CKD-associated impairment of the gut epithelial

barrier structure and function and alteration of intestinal microbiota: a- the rise in urea concentration in the body fluids and its heavy influx into the gastrointestinal tract leading to the dominance of urease-possessing bacteria, conversion of urea to ammonia [$\text{CO}(\text{NH}_2)_2 + \text{H}_2\text{O} \rightarrow 2\text{NH}_3 + \text{CO}_2$] and formation of ammonium hydroxide [$\text{NH}_3 + \text{H}_2\text{O} \rightarrow \text{NH}_4(\text{OH})$], b- $\text{NH}_4(\text{OH})$ -mediated disruption of the protein constituents of the junctional complex (claudin-1 and occludin) that face the lumen and seal the gap between the intestinal epithelial cells.¹⁹ c- paracellular translocation of endotoxin, noxious microbial, and other waste products from the lumen to the intestinal wall and systemic circulation resulting in local and systemic inflammation.²⁰⁻²² d- dietary restriction of potassium-rich nutrients (to prevent hyperkalemia) including fruits and vegetables which are common sources of indigestible soluble and insoluble complex carbohydrates. The indigestible complex carbohydrates are the primary source of nutrients for the gut's symbiotic bacteria that convert them to short chain fatty acids (SCFAs). These SCFA are vital nutrients for the colonic epithelial cells and the regulatory T lymphocytes (T-reg). T-reg are essential for the maintenance of the immunological self-tolerance and limitation of the inflammatory response.²³ Therefore, reduction of dietary fermentable fiber can suppress the SCFA-forming bacterial population which can, in turn, contribute to epithelial cell injury and depletion of T-reg lymphocytes. In fact, earlier studies have demonstrated significant reduction of the T-reg cell population^{24,25} and depletion of SCFA-producing bacterial families in ESRD patients.¹⁸ Given the critical role of dietary fiber in protection of symbiotic microbiota and production of SCFA, commonly prescribed dietary restriction of potassium-rich fruits and vegetables can contribute to the systemic inflammation in ESRD population. In fact, recent studies have demonstrated restoration of colonic epithelial tight junction, reversal of endotoxemia, attenuation of local and systemic inflammation, dramatic improvements in colonic microbial dysbiosis as well as composition of plasma, urine, and colonic metabolites in the CKD rats fed a diet enriched with maize amylose resistant starch (HAM-RS2)] compared to those fed a low fiber diet.^{26,27} In view of the favorable impact of the amylose-rich diet in

Table 1 Demographic characteristics of patients

	HAM-RS2 (n = 22)	Placebo (n = 22)	P value
Age (years)	52 ± 11	60 ± 14	0.04
Gender (M/F)	12/10	16/6	0.21
Body weight (kg)	64 ± 10	65 ± 11	0.37
Height (m)	1.65 ± 0.16	1.66 ± 0.09	0.79
Body mass index (BMI)	23.76 ± 2.4	23.28 ± 1.7	0.44
Systolic blood pressure (mmHg)	125.5 ± 22.5	114.5 ± 31.5	0.18
Diastolic blood pressure (mmHg)	75 ± 9	79 ± 11	0.19
HD duration (years)	5.12 ± 1.25	4.78 ± 1.75	0.46

Data are shown as mean ± SD.

attenuating systemic inflammation, oxidative stress, and other adverse manifestations of CKD in experimental animals, the present study was undertaken to test the hypothesis that resistant starch supplementation may attenuate oxidative stress, and inflammation in ESRD patients maintained on hemodialysis.

METHODS

Study design

The study was a double-blind, randomized, parallel, placebo-controlled trial designed to examine the effect of consumption of resistant starch vs. placebo on biomarkers of inflammation and oxidative stress in ESRD patients maintained on chronic hemodialysis. The study was conducted between November 2016 and February 2017 at 29 Bahman Hemodialysis center in Tabriz, Iran. The study protocol was approved by the Human Subjects Institutional Review Board at Tabriz University of Medical Sciences, Tabriz, Iran (IR.tbzmed.rec.1395.1286) and conducted in accordance with the Declaration of Helsinki and registered on the Iranian Registry of Clinical Trials (IRCT2016062628644N1). Informed consent was obtained from all participants.

The patients were randomly assigned to receive 20 g/day during the first four weeks and 25 g/day during the second four weeks of either HAM-RS2 or regular wheat-flour prepared as biscuits prepared by Araspar Benis Inc (Tabriz, Iran). The HAM-RS2 which contains 60% resistant starch was purchased from Ingredient ANZ Pty Ltd (Lane Cove, NSW, Australia). The biscuits were ingested during hemodialysis and at home between meals.

Patients

Forty-six adult ESRD patients were enrolled in the study. All participants were maintained on chronic hemodialysis

thrice weekly for at least six months. Patients who had diabetes, gastrointestinal disease, active inflammatory disorders, infections and malignancy, and patients who had received antibiotic three months prior to enrollment were excluded from the study. The underlying causes of ESRD in the study population included hypertensive nephrosclerosis in 28 patients, glomerulonephritis in eight patients, chronic interstitial nephropathy in six patients, polycystic kidney disease in one, and CKD of unknown etiology in three patients. Patients were randomized to receive HAM-RS2 or placebo. The patients in HAM-RS2 and placebo groups were on the similar medications including erythropoietin, iron, multivitamins, antihypertensive agents, and phosphate binders. Data on bowel habits and gastrointestinal symptoms were collected by a questioner. Medical Outcomes Study Questionnaire including Kidney Disease and Quality of Life (KDQOL™-360) was filled for each patient. The body mass index (BMI) was calculated using the following formula: wt/ht² (weight/height). The clinical and demographic data are summarized in Table 1.

Laboratory tests

Approximately, 15 mL of the peripheral blood samples were collected before, at four weeks and eight weeks after the onset of the study. All samples were taken in the morning in fasting state before hemodialysis procedure. The blood samples were immediately centrifuged at 3000 rpm for 10 minutes, serum was separated and divided in two aliquots. The first set was processed for determination of urea nitrogen, creatinine, uric acid, glucose, calcium, phosphorus, alkaline phosphatase lipids, and iron concentrations. The second set was stored at -80° and processed for measurements of TNF- α , interleukin-1 β (IL-1 β), IL-6, hs-CRP and malondialdehyde (MDA) concentrations, and total anti-oxidant activity. In addition, whole blood samples were used to measure

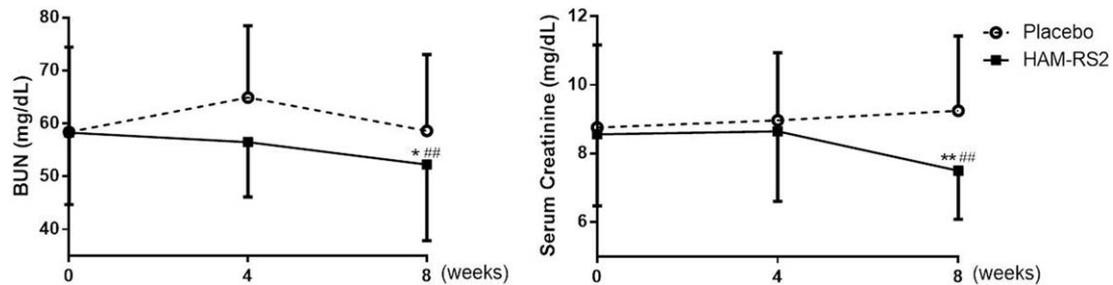


Figure 1 Serum concentrations of urea nitrogen (BUN) and creatinine in placebo and HAM-RS2-treated groups measured before and at weeks 4 and 8. * $P < 0.05$, ** $P < 0.01$ compared with week 0, ## $P < 0.01$ compared with placebo group.

hematocrit, hemoglobin and complete blood cell count. CBC, blood urea nitrogen (BUN), serum creatinine, uric acid, lipids, glucose, calcium, phosphorus, alkaline phosphatase, and iron status were measured by hospital's central laboratory.

Serum concentrations of IL-1 β , IL-6, and TNF- α , were measured using an Elisa kits purchased from the Bioassay Technology Laboratory, Shanghai, Crystal Day Biotech Co Ltd., Shanghai, China. The hs-CRP concentration was determined using an immune turbidimetric assay (BIOSYSTEMS SPANIA, Barcelona, Spain). The serum total antioxidant (TAO) activity was measured by colorimetric method (TAS kit, RANDOX Inc. Crumlin UK) using an automatic analyzer (Abbott model Alcyon 300, Lake Bluff, Illinois USA). MDA level was measured using the thiobarbituric acid reactive substances method. The MDA was used as a biomarker of oxidative stress and redox status.

Statistical analysis

Statistical analysis was performed using SPSS version 19 for Windows (SPSS, Chicago, IL, USA). Normal distribution of data was verified with the Kolmogorov–Smirnov test. To normalize the data distribution, a logarithmic conversion was used (i.e., IL1 β). Between-group comparisons of routine blood tests were carried out by one way Repeated Measures ANOVA. In addition, Analysis of covariance (ANCOVA) was used for comparing markers of inflammation and redox status (IL1 β , IL 6, TNF α , MDA, TAS, and hs-CRP) before and after the intervention between the study groups. The baseline levels were considered as covariate in Repeated Measures ANOVA and ANCOVA. Bonferoni adjustment for multiple comparisons was used for the post hoc analyses. All the tests were performed two-sided and a P values < 0.05 were considered statistically significant.

RESULTS

Clinical data

Two patients withdrew from the study after randomization. One patient from HAM-RS2 group because of gastrointestinal intolerance and one patient from control group due to admission to the hospital. The remaining 44 patients (22 patients in each group) completed the study period (eight weeks). Clinical and demographic data are provided in Table 1.

No significant difference was found in the interdialysis weight gain; 2.65 kg vs. 2.45 kg in the HAM-RS2 group and 2.42 kg vs. 1.99 kg in placebo group, before and at the end of the study, respectively. Likewise, no significant difference was observed in the mean BMI before and at the end of the study in HAM-RS2 group (23.76 and 23.28) and placebo-treated group (22.92 and 21.41). The frequency of bowel movements in the HAM-RS2 and control groups (3.5 and 3.6 per week) was similar during the four weeks prior the onset of study but increased in the HAM-RS2 compared with the control group (4.2 and 3.7 per week) at the end of study. Data derived from the Medical Outcomes Study Questionnaire including KDQOLTM-360 showed no significant change during the study in either HAM-RS2 or control group. Only one patient from HAM-RS2 group had severe side effect with epigastric pain and vomiting after administration of high amylose diet necessitating discontinuation of the diet. This patient was excluded from study. There was mild to moderate side effects including abdominal distention in five patients from HAM-RS2 group and two patients from control group and increasing the number intestinal transit in some HAM-RS2 consuming patients.

General laboratory data

Data are shown in Figure 1 and Table 2. No significant changes were observed in serum urea and creatinine

Table 2 General laboratory data in placebo (n = 22) and HAM-RS2-treated groups (n = 22)

Weeks	Placebo			HAM-RS2		
	0	4	8	0	4	8
Hematocrit (%)	36.0 ± 3.4	35.9 ± 4.6	39.0 ± 10.7	35.5 ± 3.3	37.1 ± 3.0	37.5 ± 3.3
Phosphorus (mg/dL)	4.94 ± 1.1	4.76 ± 0.8	5.26 ± 1.0	4.37 ± 0.9	4.56 ± 1.0	4.64 ± 0.7
Calcium (mg/dL)	8.54 ± 0.6	8.53 ± 0.4	8.43 ± 1.3	8.44 ± 0.5	8.37 ± 0.4	8.63 ± 0.3
Alk phosphatase (U/L)	5.3 ± 0.6	5.3 ± 0.7	4.9 ± 1.0	5.0 ± 0.6	5.0 ± 0.7	4.9 ± 0.5
iPTH (ng/dL)	328.2 ± 249.9	—	320.1 ± 260.5	384.7 ± 246.6	—	331.7 ± 312.4
Albumin (g/dL)	4.5 ± 0.2	—	4.3 ± 0.3	4.4 ± 0.4	—	4.3 ± 0.2
Cholesterol (mg/dL)	163.3 ± 36.8	—	146.1 ± 37.9	155.8 ± 37.5	—	159.1 ± 42.4
Triglycerides (mg/dL)	142.2 ± 87.0	—	140.2 ± 73.4	143.9 ± 65.8	—	154.1 ± 69.1
HDL-chol (mg/dL)	46.2 ± 14.6	—	44.7 ± 13.1	44.1 ± 8.0	—	45.7 ± 10.8
Ferritin (ng/mL)	348.4 ± 261.4	—	361.2 ± 196.0	278.8 ± 236.9	—	279.7 ± 212.4
Uric acid (mg/dL)	7.8 ± 1.0	—	7.1 ± 1.1 ^a	7.1 ± 1.1 ^b	—	6.59 ± 1.0 ^{a, c}

Data are shown as Mean ± SD.

^aWeek 8 vs. week 0 within groups.

^bTreated vs. untreated at week 0.

^cTreated vs. untreated at week 8.

ALP = alkaline phosphatase; iPTH = intact parathyroid hormone; Hct = hematocrit; HDL-chol = high density lipoprotein-cholesterol.

concentrations during the study period in placebo group. However, HAM-RS2 group exhibited a significant time-dependent reduction in serum urea and creatinine concentrations ($P < 0.05$). No significant changes were found in other laboratory values including Hb, Hct, serum potassium, iron, ferritin, TIBC, intact PTH, total cholesterol, HDL cholesterol, or triglyceride, during the study period in either group.

Inflammatory and oxidative biomarkers

Data are shown in Figure 2. Serum concentrations of TNF- α , IL-6, and MDA were significantly reduced in the HAM-RS2-treated group but remained unchanged in the placebo-treated group. No significant changes were found in serum IL-1 β and hs-CRP concentrations and TAO activity in the study population during the observation period.

DISCUSSION

To our knowledge, only one study reported by Xie et al. has examined the effects of a fermentable soluble dietary fiber on inflammatory status in hemodialysis patients. The authors demonstrated significant reduction of serum IL-6, IL-8, and hs-CRP with no significant change in TNF- α in dialysis patients receiving two different doses of a soluble fiber (10 g/day and 20 g/day) for six weeks when compared with control group.²⁸ The results of the present study revealed significant reduction of the inflammatory

and oxidative markers in HAM-RS2 treated dialysis patients confirming the salutary effects observed in CKD rats.^{26,27} The results of our study and the study by Xie et al., point to the beneficial effects of the high fiber diet in ESRD patients. In a recent study Sirich et al.²⁹ found that increasing dietary fiber with resistant starch supplementation for six weeks significantly reduced plasma levels of the gut microbial-derived uremic toxins, free indoxyl sulfate and to a lesser extent *p*-cresol sulfate in ESRD patients. In addition, treatment of hemodialysis patients with an escalating dose of oligofructose-enriched inulin for four weeks has been shown to reduce serum concentration of the uremic toxin, *p*-Cresyl sulfate.³⁰ In a retrospective analysis of the data from participant in the National Health and Nutrition Examination Survey III, Krishnamurthy et al.³¹ found that for each 10-g/day increase in total fiber intake, the odds of elevated CRP levels were reduced by 38% in those with kidney disease and 11% in those without kidney disease. They also found that dietary total fiber intake was inversely related with mortality in patients with kidney disease. In addition several studies have shown the association of high dietary fiber intake with lower serum IL-6, TNF- α receptor2, and CRP levels in general population and postmenopausal women.^{32–35}

The mechanism by which resistant starch supplementation attenuated systemic inflammation in our ESRD patients is not clear. However, amelioration of the uremia-induced disruption of the colonic epithelial barrier and improvement of bacterial dysbiosis with amylose

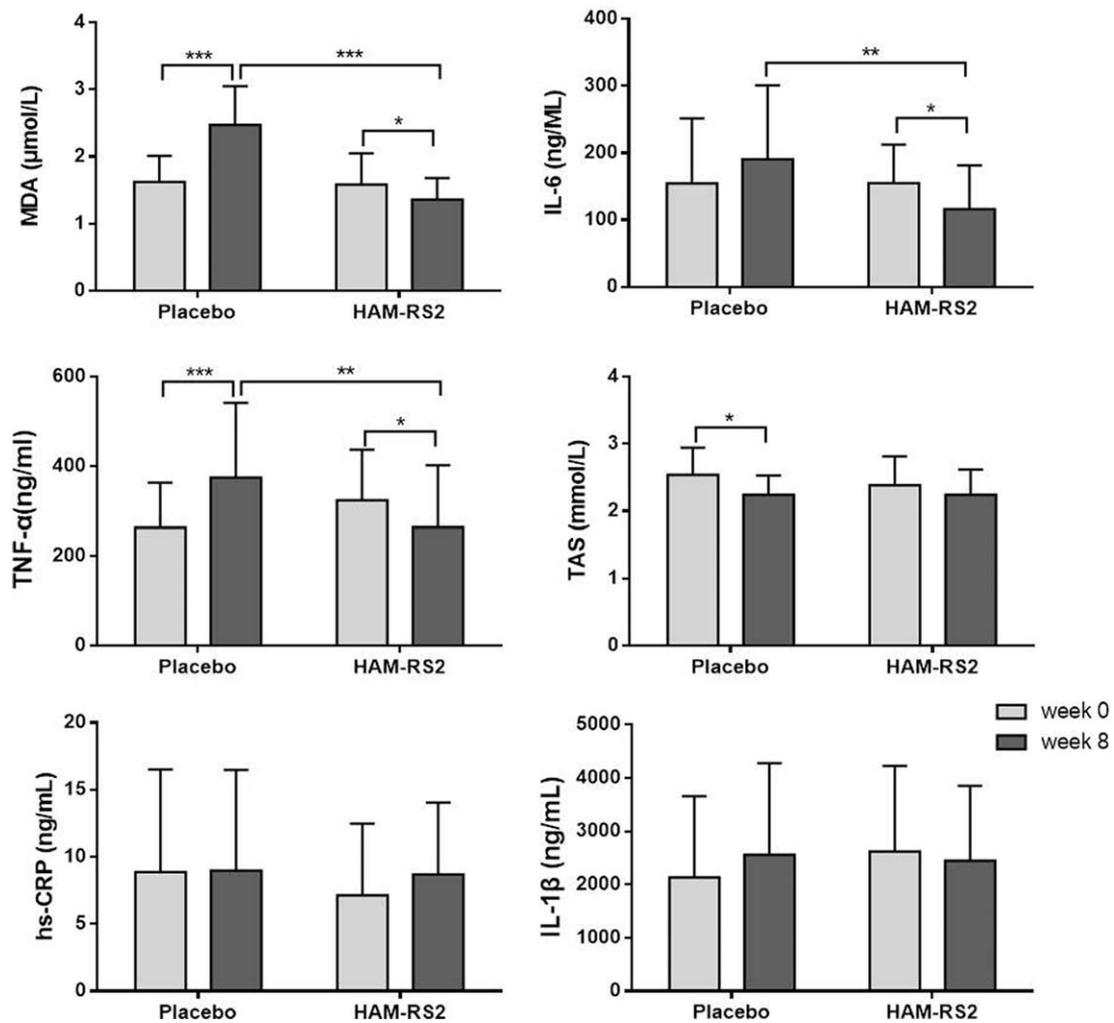


Figure 2 Serum concentrations of malondialdehyde (MDA), interleukin-6 (IL-6), tumor necrosis factor- alpha (TNF- α), total antioxidant status (TAO), high sensitivity C-reactive protein (hs-CRP), and interleukin-1beta (IL1-B), obtained in placebo and HAM-RS2-treated groups (n = 22) at the beginning and the end of the study period. *P < 0.05, **P < 0.01, and *** P < 0.001.

resistant starch-enriched diet found in CKD animals^{26,27} can, in part, account for the reduction in serum biomarkers of inflammation in our ESRD patients. SCFA produced from fermentation of unabsorbable complex carbohydrates by symbiotic bacteria in colon constitute a main source of food for colonic epithelial cells³⁶ and anti-inflammatory regulatory T lymphocytes.²³ Moreover, by inhibiting activation of NF κ B, the master regulator of inflammatory cytokines and chemokines, SCFA particularly butyric acid mitigate inflammation.³⁷ Consequently, consumption of unabsorbable complex carbohydrates which increases generation of SCFAs in the colon, plays a major role in protection of colonic epithelial barrier

structure and the body's anti-inflammatory capacity. In fact, earlier studies have shown depletion of the SCFA producing bacteria in the guts of ESRD patients and obese diabetic women³⁸ and their restoration with amylose-enriched diet in CKD animals (31). HAM-RS2 supplementation has been shown to increase population of symbiotic anti-inflammatory bacteria including Bifidobacterium and Faecalibacterium prausnitzii.³⁹

Oxidative stress is a common feature and a major mediator of cardiovascular disease and many other complications of CKD.⁶ It is caused by CKD-induced increase in generation of reactive oxygen, nitrogen, and halogen species and impaired antioxidant defense system.^{6,39} Serum

level of MDA, a commonly used biomarker of oxidative stress, significantly decreased in our amylose-treated patients and increased in the control group. Consistent with the results of our study amylose supplementation has been shown to significantly lower serum MDA in women with type 2 diabetes.⁴⁰ Taken together these findings point to efficacy of amylose supplementation in ameliorating oxidative stress.

Constipation and fluid overload are among common complications of advanced CKD.⁴¹ It is well established that by trapping water in the colon, high fiber intake can relieve constipation and improve bowel habits.⁴² In fact, increased dietary fibers has been shown to relieve constipation in diabetic patients and CKD animals.^{26,43} However, fermentation of fiber in the colon produces gases including hydrogen and methane which cause flatulence and abdominal discomfort. A potential advantage of resistant starch over oligofructose-enriched inulin and other oligosaccharides is that its slower fermentation caused by its high molecular weight limits flatulence and other gastrointestinal side effects.⁴⁴ Consistent with above study consumption of amylose was well tolerated and significantly improved the prevailing constipation in our patients.

Our HAM-RS2-treated patients exhibited a significant reduction in serum concentrations of nitrogenous waste products including BUN and creatinine. In a recent study Sirich et al.²⁹ found an insignificant reduction of serum urea nitrogen levels in their hemodialysis patients who received amylose for six weeks. This was assumed to be due to enhanced fecal nitrogen excretion. The mechanism for the observed reduction of serum urea and creatinine in our HAM-RS2-treated ESRD patients is not clear. However, the following factors may contribute to this phenomenon: A- Urea which floods the intestinal tract in uremic patients is converted to ammonia by urease-possessing microorganisms whose population is dramatically expanded in this patient population (20) [$\text{NH}_2\text{—CO—NH}_2 + \text{H}_2\text{O} \rightarrow \text{CO}_2 + 2\text{NH}_3$]. NH_3 is converted to ammonium hydroxide [$\text{NH}_3 + \text{H}_2\text{O} \rightarrow \text{NH}_4\text{OH}$] which raises the luminal PH and mediates the disruption of epithelial tight junction.¹⁹ By facilitating entry of noxious luminal contents in the systemic circulation, disruption of colonic epithelial barrier contributes to systemic inflammation which by intensifying catabolic state promotes wasting and increases urea generation. Thus, attenuation of systemic inflammation with HAM-RS2 consumption shown here and in CKD animals²⁶ can, in part, account for the reduction in serum urea level. In fact, consumption of fermentable complex carbohydrates has been shown to exerts a urea-lowering effect in normal and nephrectomized rats,⁴⁵ B- Due to dietary restrictions, population of symbiotic SCFA forming bacteria

is markedly reduced in ESRD patients.¹⁸ Fermentation of indigestible complex carbohydrates by those bacteria results formation of SCFAs which can trap ammonia and prevent its uptake and conversion to urea by the liver. This phenomenon can further contribute to the urea lowering effect observed in our HAM-RS2 ESRD patient and in CKD animals.²⁶ C- Earlier studies have demonstrated marked increase in secretion of creatinine (51) by colonic epithelium in CKD animals. Consumption of lactulose has been shown to further enhanced fecal excretion of nitrogenous waste products, favorably change microbiome and attenuate inflammation in patients with CKD.^{46,47} Therefore, enhanced viability of colonic epithelium with consumption of HAM-RS2 can, in part, contribute to unloading of waste products and its lower serum concentration, and D- The slow transit rate of colonic contents marked by constipation which is a common feature of CKD can limit intestinal secretion of creatinine by lowering their concentration gradient and reducing the liquidity of the medium which is essential for secretion of solutes by epithelial cells.

This study has some limitations including the relatively small size of the study population and short duration of the study. Future studies are needed to explore the long-term impact of dietary amylose supplementation on clinical outcomes in a large ESRD population. In addition, the other restriction of this study was difference in age range between two groups.

In conclusion, this study demonstrated that dietary supplementation with high amylose resistant starch can ameliorate inflammation and oxidative stress, lower plasma concentration of nitrogenous waste products, and improve constipation in ESRD patients maintained on hemodialysis. Given the central role of systemic inflammation and oxidative stress in the pathogenesis cardiovascular and other complications of CKD, long-term studies are needed to explore the impact of amylose supplementation on clinical outcomes in this vulnerable population.

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