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Randomized Trial of Dietary Acid Reduction and Acid-Base Status of Patients With CKD and Normal Estimated GFR

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Introduction: Modern acid-producing diets in patients with stage G3 to G5 chronic kidney disease (CKD) can cause severe acid accumulation with metabolic acidosis and less severe accumulation causing eubicarbonatemic acidosis in stages G2 to G3, each with kidney injury. The impact of these diets on acid accumulation in those with CKD but normal estimated glomerular filtration rate (eGFR) (CKD G1) is unclear.

Methods: We assessed whether acid accumulation occurs in patients with CKD and normal eGFR, and if added base-producing fruits and vegetables (F&Vs) or oral sodium bicarbonate ($NaHCO_3$) (HCO_3^-) reduces acid accumulation and/or lowers kidney injury. We randomized 153 participants with macroalbuminuric, nondiabetic, CKD stage G1 (mean eGFR = 101 ml/min per 1.73 m^2) with hypertension-associated CKD to receive F&Vs in amounts to reduce dietary acid intake by 50% (F&V, $n = 51$), oral $NaHCO_3$ to match alkali intake of F&V (HCO_3^-, $n = 51$), or usual care (UC, $n = 51$) for 5 years. We assessed acid accumulation by comparing observed to expected increase in plasma total CO_2 ($PTCO_2$) in response to retained bicarbonate (dose − urine bicarbonate excretion) 2 hours after an oral $NaHCO_3$ bolus.

Results: Baseline acid accumulation, eGFR, urine excretion of albumin, N-acetyl-β-D-glucosamine, and angiotensinogen were not different among groups. Five-year acid accumulation (mean [SD]) was lower in F&V (−1.2 [11.0] mmol] and in HCO_3^- (−1.7 [10.8] mmol) than in UC (5.2 [10.3] mmol, $P < 0.003$), which is consistent with lower acid accumulation in F&V and HCO_3^-. Five-year urine excretion of albumin, N-acetyl-β-D-glucosamine, and angiotensinogen were lower in F&V and HCO_3^- than in UC, which is consistent with less kidney injury.

Conclusions: Dietary acid reduction reduces acid accumulation and kidney injury in patients with CKD and normal eGFR.

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Diet contributes to chronic disease onset and its outcomes,[1] including CKD[2] and cardiovascular disease (CVD).[3] Among dietary aspects associated with kidney and cardiovascular outcomes is its acid- or base-producing capacity. Animal-sourced foods yield metabolic (or "fixed") acid when metabolized; most plant-sourced foods, including F&Vs, yield base.[4] Most modern diets are net acid-producing[4,5] because they contain more animal-sourced than plant-sourced foods such as F&Vs.[4,6] Such diets can cause acid accumulation sufficient to reduce serum HCO_3^- below normal for clinical laboratories, that is, cause metabolic acidosis.[7] These diets can cause metabolic acidosis in individuals with CKD and severe reductions (< 25% of normal) of eGFR.[8] Dietary acid reduction by adding base-producing F&Vs can improve metabolic acidosis in patients with CKD.[9]

Acid-producing diets also cause acid accumulation that is not enough to reduce serum HCO_3^-, that is, not cause metabolic acidosis.[5] This clinically inapparent acid accumulation is variously called eubicarbonatemic acidosis,[10,11] preclinical acidosis,[12] or subclinical

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acidosis.[13] This "covert acidosis" has been identified in patients with CKD and less severe eGFR reductions, including CKD stage 2[14–17] and stage 3.[17] It is associated with decreased bone[18] and muscle[19] health, faster CKD progression,[15] and increased CVD risk.[20] Dietary acid reduction with F&Vs[16] or oral $NaHCO_3$[14,15] reduced this clinically inapparent acid accumulation.

Whether modern acid-producing diets cause acid accumulation in patients with CKD and normal eGFR is uncertain. Short-term (days to weeks) external balance studies in healthy participants with presumably normal GFR given mineral acid while housed in research facilities show both zero (i.e., no acid accumulation)[21] and positive (i.e., acid accumulation) acid balance.[22–24] Internally assessed acid accumulation was positive in patients with CKD and normal eGFR who ate modern acid-producing diets[17]; however, whether dietary acid reduction reduced acid accumulation was not reported. Such diets in general populations, most of whom presumably do not have reduced GFR, are associated with increased CKD incidence[25,26] and faster progression.[27,28] Therefore, even small amounts of acid accumulation from acid-producing diets might threaten kidney health in patients with CKD and normal eGFR.

Here, we assessed the following: (i) internally determined acid accumulation in participants with macroalbuminuric primary hypertension-associated CKD and normal eGFR; (ii) whether if F&V or $NaHCO_3$ is added to their baseline, modern acid-producing diets yield a less acid systemic acid-base status; and (iii) differential effects of F&V or $NaHCO_3$ on kidney outcomes for these participants followed-up for 5 years in their lived environments.

METHODS

Ethics and Inclusion Statement

Written informed consent was obtained for study participation. All study activities were conducted at the Texas Tech University Health Sciences Center with institutional review board approval #L96-104.

Study Design

This trial ("Dietary acid reduction and progression of chronic kidney disease," NCT06046924) followed a prospective, randomized parallel 3-arm design. We randomized eligible individuals to 1 of 3 treatment arms in 1:1:1 ratio as follows: (i) provision of base-producing F&Vs to reduce dietary acid production[9,16,29–31]; (ii) prescription of $NaHCO_3$ tablets (HCO_3^-) by study investigators (not participant primary care clinicians who were unaware of treatment arm assignment), to match the alkali content of added F&Vs (see below); (iii) or UC. Once a participant met criteria and consented, the head study coordinator serially randomized participants to F&V, then HCO_3^-, then UC in this order without blocking.

Study Population

One hundred fifty-three study participants fitting the inclusion/exclusion criteria were recruited from Texas Tech University Health Sciences Center Clinics over 11 years to participate in a 5-year study of kidney and cardiovascular health. Eligible participants were identified by an added system feature that automatically requested urine albumin-to-creatinine ratio (UACR, mg/g) for patients diagnosed with hypertension. After enrollment and assignment, participants continued primary care follow-up. Primary care clinicians managed participants' medical concerns, notably hypertension and albuminuria, as per recommendations for hypertension[32] and albuminuria[33] at study initiation. The Texas Tech University Health Sciences Center formulary had enalapril as its only anti–angiotensin II drug for kidney protection and atorvastatin as its only statin for cardiovascular protection. Because macroalbuminuria puts participants at increased risk for progression of CKD[34–36] and subsequent CVD,[37,38] all participants were prescribed with enalapril (minimum 5 mg daily) and atorvastatin (minimum 10 mg daily) as per study protocol. The participants were treated toward systolic blood pressure goal < 130 mm Hg.[33] Primary care clinicians used their clinical judgement as to medication dosage adjustments.

Inclusion and Exclusion Criteria

Potential participants were identified through Texas Tech University Health Sciences Center clinic system chart reviews. Inclusion criteria were as follows: (i) nonmalignant hypertension; (ii) aged 18–70 years; (iii) UACR $\geq$ 200 mg/g or "macroalbuminuria"[33] assessed when recruitment began; this albuminuria level identifies participants with established CKD,[39] at increased risk for CKD progression,[34–36] and was chosen to optimize the opportunity to see a kidney-protective effect of the 2 dietary acid reduction strategies; (iv) eGFR $\geq$ 90 ml/min per 1.73 m^2, that is, CKD stage 1 or normal eGFR[39] to study participants with early CKD for whom kidney-protective interventions are likely to be most beneficial[40]; (v) $PTCO_2 \geq 22$ mmol, that is, no metabolic acidosis; (vi) $\geq$ 2 primary care visits in the preceding year, showing compliance; (vii) able to provide informed consent. Exclusion criteria include the following: (j) malignant hypertension or history thereof; (ii) primary kidney disease or findings consistent thereof such as 3 red blood cells per high-powered field of urine or urine cellular casts; (iii) history of diabetes or fasting blood glucose $\geq$ 110 mg/dl; (iv) history of hematologic disorders, malignancies,

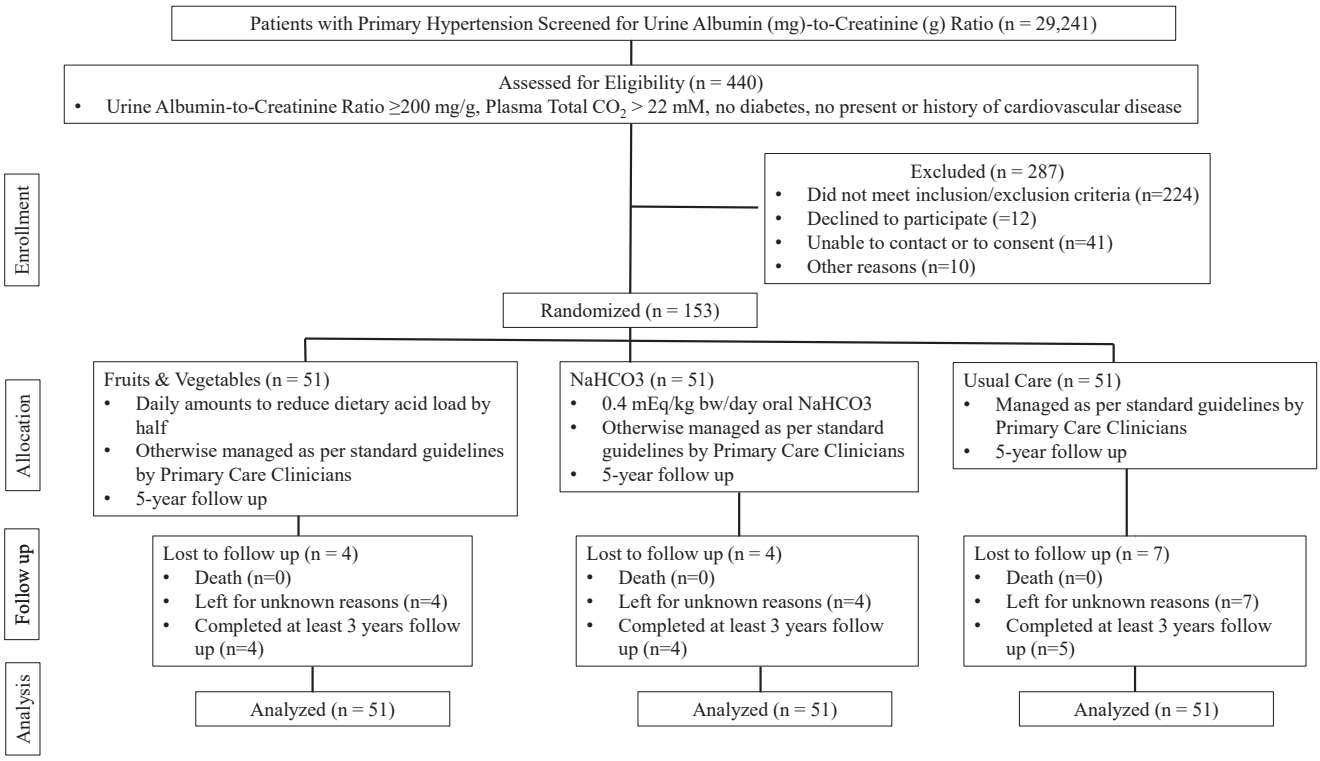

Figure 1. CONSORT diagram. $PTCO_2$, plasma total CO_2 (slightly higher than bicarbonate concentration).

chronic infections, current pregnancy, history or clinical evidence of CVD; (v) peripheral edema or diagnoses associated with edema such as heart or liver failure or nephrotic syndrome because of the sodium load with $NaHCO_3$ therapy; (vi) unable to provide informed consent.

Participant Screening and Recruitment

Over 11 years, 29,241 clinic patients with primary hypertension diagnosis were screened for UACR. The CONSORT diagram (Figure 1) shows that 440 (1.5%) had UACR $\geq$ 200 mg/g, $PTCO_2$ > 22 mmol, and no CVD or history thereof. We randomized 51 each to F&V, HCO_3^-, and UC. The study protocol described in the Supplementary Material has further details. We chose participants with hypertension-associated CKD because its pathology more closely resembled that of partial nephrectomy animal CKD models in basic studies[41] from which the present studies derived, than did the more common CKD cause of diabetes. To differentiate F&V effects from their base-producing capacity, we included an arm of participants prescribed with $NaHCO_3$ in

Table 1. Baseline sample demographics, clinical and laboratory measures including PRAL, Sys BP, plasma concentration of electrolytes, and prescribed dosage of medications per care guidelines

Variables at baseline, statistics	Whole Sample	UC[a]	HCO3[a]	F&V[a]	*P*-value[b]
Female, *n* (%)	78 (51)	27 (52.9)	24 (47.1)	27 (52.9)	0.790
Age, yr, M (SD)	48.84 (6.6)	49.1 (7.6)	48 (6.3)	49.5 (5.9)	0.513
Race/Ethnicity, *n* (%):					0.131
African American	72 (47.1)	22 (43.1)	22 (43.1)	28 (54.9)	
Hispanic	36 (23.5)	11 (21.6)	10 (19.6)	15 (29.4)	
Non-Hispanic White	45 (29.4)	18 (35.3)	19 (37.3)	8 (15.7)	
PRAL, M (SD)	61.7 (10.3)	61.0 (12.1)	61.4 (9.8)	62.5 (8.9)	0.763
Sys BP, M (SD)	157.5 (8.7)	157.9 (8.8)	156.5 (8.9)	158.3 (8.4)	0.549
eGFR, M(SD)	101.7 (7.5)	101.33 (8.3)	101.9 (7.3)	101.8 (7.1)	0.9169
Plasma sodium, M (SD)	139.5 (1.42)	139.4 (1.4)	139.5 (1.3)	139.6 (1.5)	0.663
Plasma chloride, M (SD)	102.9 (1.25)	102.8 (1.4)	102.9 (1.2)	102.9 (1.1)	0.924
Plasma potassium, M (SD)	4.10 (0.15)	4.1 (0.17)	4.1 (0.13)	4.1 (0.14)	0.847

eGFR, estimated glomerular filtration rate; F&V, fruit and vegetables group; M, mean; Mdn, median; $NaHCO_3$, Sodium Bicarbonate group; PRAL, potential renal acid load; Sys BP, Systolic blood pressure; UC= Usual Care group.
[a]*N* = 51 in each group at baseline.
[b]*P*-value is for chi-square distribution associated with the cross-tabulation of group by sex and race/ethnicity; and the F-statistics from omnibus 1-way analysis of variance for continuous outcomes (age, PRAL through plasma potassium).

Table 2. Means, SD, and 95% confidence intervals for all outcomes measured annually across time in each of the groups

Outcomes	Statistics	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
				UC			
UACR	Mean	326.12	339.45	357.92	385.50	403.54	416.11
	SD	77.25	76.13	76.64	87.54	91.85	98.98
	LL–UL	304.39–347.85	318.04–360.86	336.37–379.48	360.08–410.92	376.27–430.82	386.02–446.21
U8-iso	Mean	1.09	1.11	1.16	1.22	1.24	1.27
	SD	0.18	0.15	0.14	0.14	0.15	0.17
	LL–UL	1.04–1.14	1.06–1.15	1.12–1.20	1.18–1.27	1.20–1.28	1.21–1.32
UNAG	Mean	2.51	2.56	2.65	2.69	2.74	2.78
	SD	0.39	0.36	0.34	0.37	0.35	0.37
	LL–UL	2.39–2.62	2.46–2.66	2.55–2.74	2.59–2.80	2.64–2.85	2.67–2.90
UATG	Mean	21.47	22.19	22.71	23.01	23.11	23.09
	SD	2.76	2.46	2.66	2.81	2.66	2.67
	LL–UL	20.69–22.25	21.50–22.88	21.96– 23.46	22.19– 23.83	22.32–23.90	22.28–23.90
PRAL	Mean	61.10	61.08	62.04	60.10	60.33	60.43
	SD	12.12	11.42	10.74	10.19	10.18	9.64
	LL–UL	57.69–64.51	57.87–64.29	59.02–65.06	57.15–63.06	57.30–63.35	57.50–63.36
$PTCO_2$	Mean	26.41	26.50	26.40	26.36	26.36	26.24
	SD	0.83	0.78	0.68	0.55	0.51	0.59
	LL–UL	26.18–26.65	26.29–26.72	26.21–26.59	26.20–26.52	26.21–26.51	26.06–26.42
$PHCO_3^-$	Mean	25.2451	25.2059	25.1078	25.0687	25.0630	25.0318
	SD	0.7981	0.7763	0.6740	0.5520	0.5039	0.5854
	LL–UL	25.0206–25.4696	24.9876–25.4242	24.9183–25.2974	24.9085–25.2290	24.9134–25.2127	24.8538–25.2098
PCO_2	Mean	41.1843	41.1510	41.0529	41.0042	41.0174	40.8614
	SD	1.1429	1.0565	0.8785	0.7754	0.7646	0.8635
	LL–UL	40.8629–41.5058	40.8538–41.4481	40.8059–41.3000	40.7790–41.2293	40.7903–41.2444	40.5988–41.1239
PpH	Mean	7.4073	7.4068	7.4060	7.4062	7.4058	7.4070
	SD	0.0055	0.0062	0.0070	0.0066	0.0076	0.0076
	LL–UL	7.4057–7.4088	7.4051–7.4086	7.4041–7.4080	7.4043–7.4081	7.4036–7.4081	7.4047–7.4093
Pcit	Mean	0.1582					0.1571
	SD	0.0110					0.0099
	LL–UL	0.1551–0.1613					0.1541–0.1601
8h UcitV	Mean	1.1458					1.1241
	SD	0.0323					0.0420
	LL–UL	1.1367–1.1549					1.1113–1.1369
UV/Pcit	Mean	0.0152					0.0149
	SD	0.0011					0.0012
	LL–UL	0.0149 –0.0155					0.0146–0.0153
8h UNAE	Mean	25.2490					25.6523
	SD	2.4767					3.1327
	LL–UL	24.5524–25.9456					24.6998–26.6047
8h UNH_4^+V	Mean	14.9647					14.9705
	SD	1.5802					1.4168
	LL–UL	14.5203–15.4092					14.5397–15.4012
8h UTAV	Mean	10.2824					10.6818
	SD	1.0682					2.5232
	LL–UL	9.9819–10.5828					9.9147–11.4489
8h $UHCO_3V$	Mean	0.1933					0.1236
	SD	0.2460					0.1527
	LL–UL	0.1241–0.2625					0.0772–0.1701
Acid accumulation	Mean	3.5843					5.2250
	SD	13.9630					10.2950
	LL–UL	−0.3428 to 7.5115					2.0950–8.3550
				$NaHCO_3$			
UACR	Mean	321.06	318.73	317.29	313.48	306.46	308.17
	SD	75.23	71.44	70.01	64.29	60.48	57.40
	LL–UL	299.90–342.22	298.63–338.82	297.60–336.98	295.21–331.75	288.90–324.02	291.32–325.02
U8-iso	Mean	1.09	1.07	1.07	1.08	1.07	1.06
	SD	0.17	0.11	0.11	0.11	0.12	0.12
	LL–UL	1.04–1.14	1.04–1.10	1.04–1.10	1.05–1.11	1.04–1.11	1.03–1.10

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Table 2. (Continued) Means, SD, and 95% confidence intervals for all outcomes measured annually across time in each of the groups

Outcomes	Statistics	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
UNAG	Mean	2.49	2.49	2.47	2.45	2.45	2.47
	SD	0.31	0.30	0.29	0.29	0.33	0.32
	LL–UL	2.40–2.57	2.41–2.58	2.39–2.55	2.36–2.53	2.36–2.54	2.37–2.56
UATG	Mean	21.21	20.87	20.62	20.73	20.39	20.62
	SD	3.07	2.77	2.56	2.63	2.63	2.43
	LL–UL	20.35–22.07	20.10–21.65	19.90–21.34	19.98–21.48	19.63–21.16	19.90–21.33
PRAL	Mean	61.10	61.08	62.04	60.10	60.33	60.43
	SD	12.12	11.42	10.74	10.19	10.18	9.64
	LL–UL	57.69–64.51	57.87–64.29	59.02–65.06	57.15–63.06	57.30–63.35	57.50–63.36
$PTCO_2$	Mean	26.35	26.58	26.61	26.66	26.71	26.68
	SD	0.77	0.62	0.62	0.65	0.61	0.55
	LL–UL	26.14–26.57	26.41–26.76	26.43–26.78	26.48–26.85	26.54–26.89	26.52–26.84
$PHCO_3^-$	Mean	25.0706	25.2843	25.3059	25.3620	25.4313	25.3809
	SD	0.7619	0.6143	0.6227	0.6442	0.6298	0.5472
	LL–UL	24.8563–25.2849	25.1115–25.4571	25.1307–25.4810	25.1789–25.5451	25.2484–25.6141	25.2202–25.5415
PCO_2	Mean	41.0843	41.3098	41.3353	41.4020	41.4917	41.4646
	SD	0.7398	0.5934	0.6085	0.6186	0.6014	0.6145
	LL–UL	40.8762–41.2924	41.1429–41.4767	41.1641–41.5065	41.2262–41.5778	41.3171–41.6663	41.2861–41.6430
PpH	Mean	7.4051	7.4066	7.4066	7.4070	7.4071	7.4065
	SD	0.0054	0.0045	0.0045	0.0047	0.0050	0.0043
	LL–UL	7.4035–7.4066	7.4053–7.4078	7.4053–7.4079	7.4056–7.4083	7.4057–7.4086	7.4052–7.4077
Pcit	Mean	0.1580					0.1581
	SD	0.0111					0.0111
	LL–UL	0.1549–0.1612					0.1550–0.1612
8h UcitV	Mean	1.1430					1.1406
	SD	0.0153					0.0160
	LL–UL	1.1387–1.1473					1.1361–1.1452
UV/Pcit	Mean	0.0151					0.0151
	SD	0.0011					0.0011
	LL–UL	0.0148–0.0154					0.0148–0.0154
8h UNAE	Mean	25.5549					15.9660
	SD	3.0545					4.1019
	LL–UL	24.6958–26.4140					14.7616–17.1703
8h UNH_4^+V	Mean	14.7451					8.6638
	SD	1.7261					2.2850
	LL–UL	14.2596–15.2306					7.9929–9.3347
8h UTAV	Mean	10.8333					7.3894
	SD	1.9947					1.8646
	LL–UL	10.2723–11.3943					6.8419–7.9368
8h $UHCO_3^-V$	Mean	0.1757					0.2064
	SD	0.1311					0.0940
	LL–UL	0.1388–0.2126					0.1788–0.2340
Acid accumulation	Mean	2.5833					−1.7170
	SD	13.6970					10.8165
	LL-UL	−1.2690 to 6.4357					−4.8929 to 1.4588
				F&V			
UACR	Mean	322.25	322.45	321.37	317.82	310.94	306.32
	SD	73.40	64.04	59.99	56.29	58.64	58.46
	LL-UL	301.61–342.90	304.44–340.46	304.50–338.25	301.99–333.65	294.27–327.61	289.15–323.48
U8-iso	Mean	1.09	1.08	1.07	1.09	1.08	1.08
	SD	0.15	0.11	0.09	0.10	0.11	0.11
	LL–UL	1.04–1.13	1.05–1.11	1.05–1.10	1.06–1.12	1.05–1.11	1.05–1.11
UNAG	Mean	2.49	2.50	2.48	2.50	2.48	2.51
	SD	0.36	0.34	0.32	0.31	0.32	0.34
	LL–UL	2.39–2.59	2.41–2.60	2.39–2.58	2.41–2.58	2.39–2.57	2.41–2.61
UATG	Mean	21.14	20.69	20.56	20.64	20.76	20.85
	SD	2.86	2.43	2.61	2.44	2.27	2.16
	LL–UL	20.33–21.94	20.01–21.38	19.82–21.29	19.96–21.33	20.12–21.41	20.22–21.49

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Table 2. (Continued) Means, SD, and 95% confidence intervals for all outcomes measured annually across time in each of the groups

Outcomes	Statistics	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
PRAL	Mean	62.53	38.00	39.67	40.63	41.52	41.83
	SD	8.73	8.74	9.27	7.93	7.43	7.51
	LL–UL	60.07–64.98	35.54–40.46	37.06–42.27	38.40–42.86	39.41–43.63	39.62–44.04
$PTCO_2$	Mean	26.37	26.54	26.62	26.70	26.71	26.70
	SD	0.67	0.64	0.63	0.67	0.59	0.54
	LL–UL	26.19–26.56	26.36–26.72	26.44–26.79	26.51–26.88	26.54–26.88	26.54–26.86
$PHCO_3^-$	Mean	25.0706	25.2255	25.3137	25.4020	25.4080	25.4000
	SD	0.6697	0.6465	0.6271	0.6659	0.5795	0.5304
	LL–UL	24.8822–25.2589	25.0437–25.4073	25.1374–25.4901	25.2147–25.5892	25.2433–25.5727	25.2443–25.5557
PCO_2	Mean	41.0137	41.1451	41.2118	41.3059	41.3300	41.2213
	SD	0.9920	0.9072	0.8887	0.8912	0.8021	0.8500
	LL–UL	40.7347–41.2927	40.8900–41.4002	40.9618–41.4617	41.0552–41.5565	41.1020–41.5580	40.9717–41.4709
PpH	Mean	7.4060	7.4073	7.4081	7.4086	7.4085	7.4094
	SD	0.0035	0.0048	0.0041	0.0048	0.0043	0.0077
	LL–UL	7.4050–7.4070	7.4060–7.4087	7.4070–7.4093	7.4073–7.4100	7.4073–7.4097	7.4071–7.4117
Pcit	Mean	0.1591					0.1595
	SD	0.0090					0.0091
	LL–UL	0.1566–0.1616					0.1569–0.1621
8h UcitV	Mean	1.1414					1.1634
	SD	0.0152					0.0774
	LL–UL	1.1371–1.1456					1.1412–1.1856
UV/Pcit	Mean	0.0150					0.0153
	SD	0.0009					0.0014
	LL–UL	0.0147–0.0152					0.0149–0.0157
8h UNAE	Mean	25.5314					17.4319
	SD	3.4992					3.5808
	LL–UL	24.5472–26.5155					16.3806–18.4833
8h UNH_4^+V	Mean	14.6490					9.5596
	SD	2.1952					1.9256
	LL–UL	14.0316–15.2664					8.9942–10.1250
8h UTAV	Mean	10.8706					8.5362
	SD	1.8878					2.4391
	LL–UL	10.3396–11.4015					7.8200–9.2523
8h $UHCO_3^-V$	Mean	0.1455					0.1950
	SD	0.0966					0.1009
	LL–UL	0.1183–0.1727					0.1657–0.2243
Acid accumulation	Mean	4.0912					−1.1894
	SD	12.7110					11.0234
	LL–UL	0.5161–7.6662					−4.4260 to 2.047

8h UcitV, 8-hour urine citrate excretion; 8h $UHCO_3^-V$, 8-hour urine bicarbonate excretion; 8h UNAE, 8-hour urine net acid excretion; 8h UNH_4^+V, 8-hour urine-ammonium excretion; 8h UTAV, 8-hour urine titratable acid excretion; eGFR, estimated glomerular filtration rate; F&V, fruit and vegetable group; LL, lower limit; $NaHCO_3$, sodium bicarbonate group; Pcit, plasma citrate concentration; PCO_2, plasma partial pressure of CO_2 gas; $PHCO_3^-$, plasma bicarbonate concentration; PpH, plasma pH; PRAL, potential renal acid load; $PTCO_2$, plasma total CO_2; Sys BP, systolic blood pressure; U8-iso, urine 8-isoprostaglandin F2α (8-iso) excretion; UACR, urine albumin-to-creatinine ratio; UATG, urine angiotensinogen excretion; UC, usual care; UL, upper limit; UNAG, urine N-acetyl-β-D-glucosamine excretion; UV/Pcit, urine citrate clearance.
n's were as follows: $n = 51$ in each group at baseline through year 2. At year 3, the *n*'s were 51 for F&V, 50 for $NaHCO_3$, and 48–49 for usual care. At year 4, *n*'s were 50 for F&V, 48 for $NaHCO_3$, and 46–47 for UC. At year 5, *n*'s were 47 for F&V, 47 for $NaHCO_3$, and 44–45 for UC.
Blank cells indicate that the indicated parameters were not collected during that year.

amounts to match the alkalizing effects of F&V. Patients with macroalbuminuria constitute only about 1% of those with primary hypertension[42,43] and those with macroalbuminuria and normal eGFR are less common than those with reduced eGFR.[43] We invested community and faith-based social resources[44,45] to promote retention of these unusual participants once enrolled.

Participant recruitment began on June 24, 1996 and the last participant was enrolled on November 15, 2006 after attaining prespecified sample size. The last enrolled participant completed follow-up on December 15, 2011. The long recruitment period is due to our focus on macroalbuminuric participants with primary hypertension and normal kidney function who are unusual. The long time since follow-up of the last participant and analysis of the data is explained by frugal use of funds from the local foundation that supported analysis of the thousands of blood and urine samples collected over 15 years. Sample measurement was interrupted for nearly 3 years when the analytic laboratory was closed due to the COVID-19 pandemic.

Clinicians of patients with UACR $>$ 20 mg/g were notified that their patients had albuminuria and were advised to begin anti–angiotensin II therapy

Table 3. The *P*-values for the group by time interaction terms from the mixed linear regressions with random intercepts for acid-base outcomes measured at baseline and annually for 5 years and those measured only at baseline and year 5 along with 95% confidence intervals for the net change from baseline to year 5 for each arm

		P-value for Time X group interaction terms					Year 5-Base Net change (LL–UL)		
Parameter	Contrasts	Year 1 - base	Year 2- base	Year 3 -base	Year 4 - base	Year 5 - base	UC	HCO3	F&V
PRAL	UC vs. HCO3	0.719	0.07	0.725	0.889	0.354	−1.3011 to 1.9000	−1.2967 to 4.0201	−23.2055 to −18.4966
	UC vs. F&V	<0.001	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	<0.001	<0.001	<0.001	<0.001	<0.001			
$PTCO_2$	UC vs. HCO3	0.138	0.005	<0.001	<0.001	<0.001	−0.3352 to 0.0625	0.1603–0.5163	0.1145–0.5110
	UC vs. F&V	0.41	0.008	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.51	0.902	0.976	0.706	0.871			
PCO_2	UC vs. HCO3	0.013	<0.001	<0.001	<0.001	<0.001	−0.4843 to −0.1157	0.2265–0.5527	−0.0431 to 0.4091
	UC vs. F&V	0.115	0.002	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.368	0.613	0.698	0.237	0.057			
$PHCO_3^-$	UC vs. HCO3	0.008	<0.001	<0.001	<0.001	<0.001	−0.3835 to 0.0153	0.1372–0.5053	0.1195–0.5103
	UC vs. F&V	0.043	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.54	0.935	0.781	0.717	0.982			
PpH	UC vs. HCO3	0.029	0.002	0.001	<0.001	0.118	−0.0022 to 0.0021	−0.0003 to 0.0032	0.0011–0.0058
	UC vs. F&V	0.052	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.81	0.527	0.455	0.514	0.03			
Acid Accumulation	UC vs. HCO3	-	-	-	-	0.002	−1.7108 to 3.9335	−7.7808 to −2.1426	−8.0203 to −2.2223
	UC vs. F&V	-	-	-	-	0.001			
	HCO3 vs. F&V	-	-	-	-	0.834			
Pcit	UC vs. HCO3	-	-	-	-	0.014	−0.0013 to 0.0000	−0.0002 to 0.0010	0.0000–0.0008
	UC vs. F&V	-	-	-	-	0.014			
	HCO3 vs. F&V	-	-	-	-	0.936			
UcitV	UC vs. HCO3	-	-	-	-	0.046	−0.0356 to −0.0116	−0.0044 to −0.0013	0.0005–0.0441
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.012			
UV/Pcit	UC vs. HCO3	-	-	-	-	0.154	−0.0013 to 0.0000	−0.0002 to 0.0010	0.0000–0.0008
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.019			
8h UNAE	UC vs. HCO3	-	-	-	-	< 0.001	−0.2502 to 1.3866	−10.4935 to −8.9363	−9.1012 to −7.0860
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.008			
8h $U_{NH4+}V$	UC vs. HCO3	-	-	-	-	< 0.001	−0.2210 to 0.4846	−6.7353 to −5.5286	−5.7648 to −4.5586
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.008			
8h $U_{TA}V$	UC vs. HCO3	-	-	-	-	< 0.001	−0.2949 to 1.1720	−3.9611 to −3.1027	−3.0640 to −1.4509
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.009			
8h $U_{HCO3^-}V$	UC vs. HCO3	-	-	-	-	0.004	−0.1265 to 0.0146	0.0052–0.0620	0.0222–0.0811
	UC vs. F&V	-	-	-	-	< 0.001			
	HCO3 vs. F&V	-	-	-	-	0.537			

8h UcitV, 8-hour urine citrate excretion; 8h $UHCO_3^-V$, 8-hour urine bicarbonate excretion; 8h UNAE, 8-hour urine net acid excretion; 8h UNH_4^+V, 8-hour urine ammonium excretion; 8h UTAV, 8-hour urine titratable acid excretion; F&V, fruit and vegetable group; HCO_3, sodium bicarbonate group; LL, lower limit; Pcit, plasma citrate concentration; PCO_2, plasma partial pressure of CO_2 gas; $PHCO_3^-$, plasma bicarbonate concentration; PpH, plasma pH; PRAL, potential renal acid load; $PTCO_2$, plasma total CO_2; UC, usual care; UcitV/Pcit, urine citrate clearance; UL, upper limit.

Table 4. The *P*-values for the group by time interaction terms from the mixed linear regressions with random intercepts for each outcome measured at baseline and annually for 5 years concerning kidney injury and 95% confidence intervals for the net change from baseline to year 5 for each arm

		P-value for Time X group interaction terms					Year 5-Base Net change (LL–UL)		
Parameter	Contrasts	Year 1 - base	Year 2- base	Year 3 -base	Year 4 - base	Year 5 - base	UC	HCO3	F&V
UACR	UC vs. HCO3	0.047	<0.001	<0.001	<0.001	<0.001	71.8–110.1	−33.0 to 0.61	−33.1 to 3.01
	UC vs. F&V	0.096	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.749	0.715	0.536	0.472	0.982			
UNAG	UC vs. HCO3	0.071	<0.001	<0.001	<0.001	<0.001	0.21–0.36	−0.06 to 0.05	−0.05 to 0.06
	UC vs. F&V	0.111	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.835	0.729	0.101	0.429	0.466			
UATG	UC vs. HCO3	<0.001	<0.001	<0.001	<0.001	<0.001	1.14–2.16	−0.77 to 0.01	−0.74 to 0.02
	UC vs. F&V	<0.001	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.668	0.976	0.852	0.166	0.761			
U8-iso	UC vs. HCO3	0.099	<0.001	<0.001	<0.001	<0.001	0.12–0.25	−0.07 to 0.01	−0.05 to 0.04
	UC vs. F&V	0.216	<0.001	<0.001	<0.001	<0.001			
	HCO3 vs. F&V	0.68	0.869	0.517	0.614	0.349			

F&V, fruit and vegetable group; HCO_3, sodium bicarbonate group; LL, lower limit; U8-iso, urine 8-isoprostaglandin F2α (8-iso) excretion; UACR, urine albumin-to-creatinine ratio; UATG, urine angiotensinogen excretion; UC, usual care; UL, upper limit; UNAG, urine N-acetyl-β-D-glucosamine excretion.
UACR *P*-values and year-5 to baseline net change 95% confidence intervals were first presented in reference # 64 and are re-presented due to its importance to interpretation of acid-base findings as they relate to progression of early-stage chronic kidney disease.

(angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) for kidney and atorvastatin for cardiovascular protection, respectively. Clinicians were similarly notified and advised of patients with macroalbuminuria who did not meet the inclusion and exclusion criteria. Patients were also made aware of their albuminuria and encouraged to discuss with their clinicians the need to reduce their risk for subsequent decline of their kidney function and for diseases of the heart and blood vessels, including heart attack and stroke.

Interventions

F&V

The F&V provision was 2 to 4 cups daily of base-producing F&Vs, depending on the base-producing capacity of F&Vs used,[4] provided in weekly allotments retrieved from church-based Farm Stands.[44] Fruits were predominantly apples, apricots, oranges, peaches, pears, raisins, and strawberries. Vegetables were predominantly carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes, and zucchini. The F&V amount was estimated to reduce potential renal acid load (PRAL)[4] (calculated from 3-day food diaries as done previously[29]) by half for the 5-year protocol. Because PRAL for the groups averaged approximately 62 mmol and average body weight for study participants was approximately 84 kg, this dietary alkali provision averaged 31 mmol/84 kg = 0.37 mmol/kg. To help ensure that participants ate their F&V allotment and did not share it among family members, the allotment calculated for each participant was multiplied by the number of household members and provided to each participant. Participants otherwise received standard care for albuminuria[33] and hypertension[32] and their other health concerns as per guidelines when these studies began.

HCO_3^-

Participants were prescribed with $NaHCO_3$ tablets 0.4 mmol/kg bw/d (average of four to five 650 mg $NaHCO_3$ tablets daily in 2 divided doses) supplied monthly for the 5-year protocol. This dose was designed to match the alkali content of the F&V provision. They otherwise received standard medical care as described.

UC

UC participants received no additional dietary acid reduction and were treated with standard medical care as described.

Measures

Plasma and urine creatinine and urine albumin were measured using the Sigma Diagnostics Creatinine Kit (Procedure No. 555, Sigma Diagnostics).[46] Plasma cystatin-C was measured with a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Somerville, NJ) with a nephelometer (BNII; Dade Bering).[47] The Modification of Diet Renal disease formula[48] for eGFR was initially used to determine eligibility for recruitment and study enrollment. Subsequently, eGFR was calculated using the CKD Epidemiology Collaboration formula.[49] We measured albuminuria as a general assessment of kidney injury and because follow-up levels associate directly with CKD progression.[50] Urine N-acetyl-β-D-glucosamine was measured using a colorimetric assay (Boehringer Mannheim, Mannheim, Germany) to assess kidney tubulointerstitial injury,[51] a major feature of hypertension-associated CKD.[52] We measured urine angiotensinogen

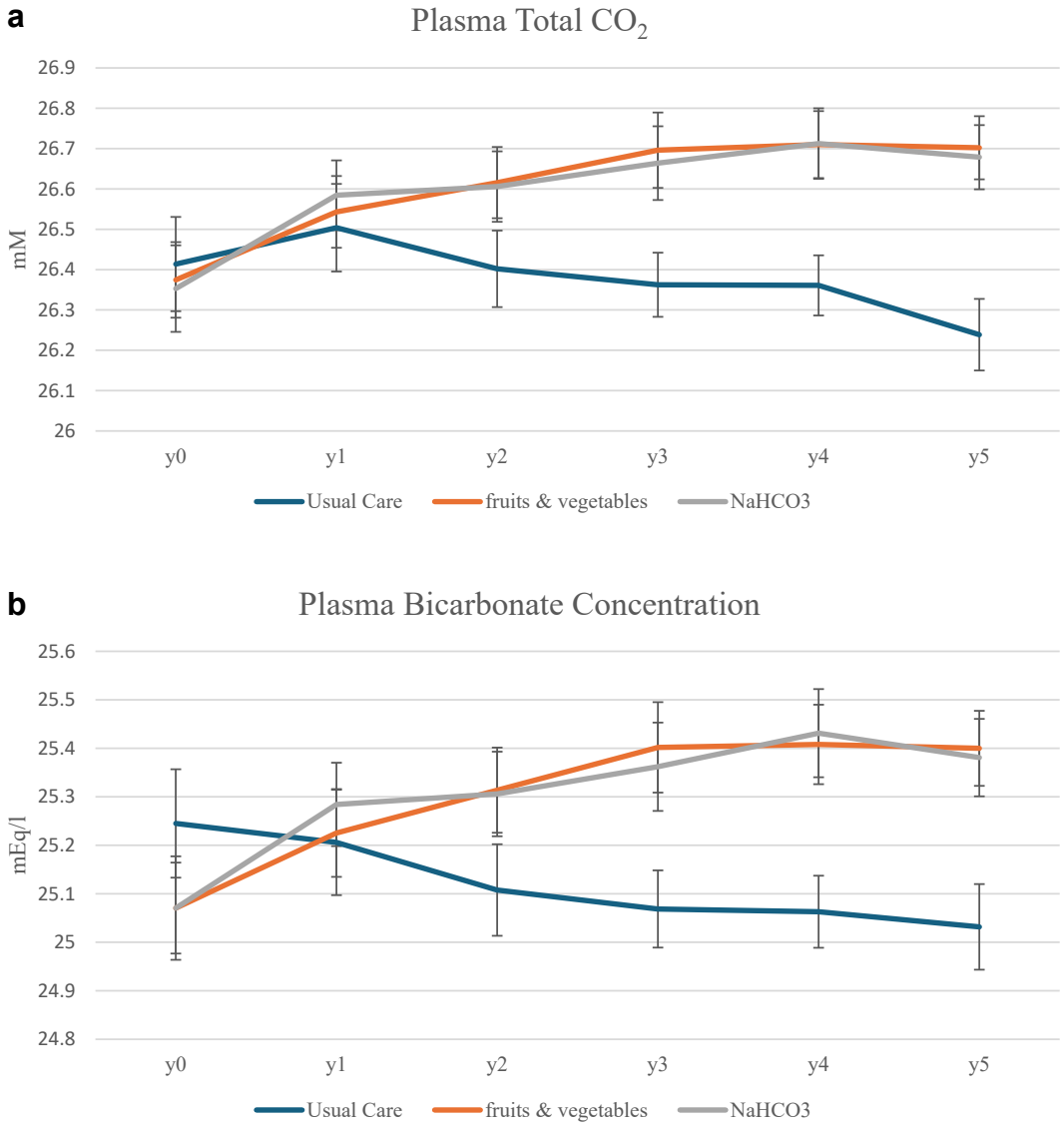

Figure 2. Trajectories for the 3 intervention groups regarding plasma acid-base outcomes that are commonly measured in clinical settings. The trajectories include cell means and standard errors measured annually from baseline through year 5 of the intervention. (a) Plasma total CO_2 ($PTCO_2$, mmol); trajectories show greater plasma total CO_2 increase in participants given fruits and vegetables or oral $NaHCO_3$ than those receiving Usual Care, evident in year 2 and later relative to baseline. (b) Plasma bicarbonate concentration ($PHCO_3^-$, mEq/l); trajectories show a greater increase in plasma bicarbonate concentration in participants given fruits and vegetables or $NaHCO_3$ than those receiving Usual Care, evident in year 2 and later relative to baseline. (Continued)

as an assessment of kidney angiotensin II levels,[53] a contributor to progression of hypertension-associated CKD.[54,55] It was measured using RIA quantitation of angiotensin I generation[53] after addition of excess exogenous porcine renin (R 2761; Sigma, St. Louis, MO) using a commercially available kit (Incstar, Stillwater, MI). Urine samples were included with renin at 37° C, removed at 0, 10, 30, 60, and 120 minutes, and diluted with reagent blank in such a way that RIA results were on the linear portion of a previously determined curve. The amount of angiotensin I produced was plotted versus time. Saturation kinetics due to conversion of all angiotensinogen to angiotensin I were obtained at 60 minutes. We measured urine total 8-iso prostaglandin F2α (U8-iso) as a gauge of systemic oxidative stress[56] that is associated with hypertension[57] and progression of hypertension-associated CKD.[54] It was extracted into the ethyl acetate phase,[58] and screened by enzyme-linked immunosorbent assay method (Procedure No. 516351, Cayman Chemical, Ann Arbor, MI). Urine levels of N-acetyl-β-D-glucosamine excretion, angiotensinogen excretion, and 8-iso in a "spot" urine were corrected for g creatinine. Parameters were measured in stored urine and plasma (for citrate) samples (−80° C).

We assessed steady state acid accumulation as the difference between expected (retained HCO_3^-/HCO_3^- space of distribution) and observed increase in $PTCO_2$ from baseline multiplied by the HCO_3^- space of

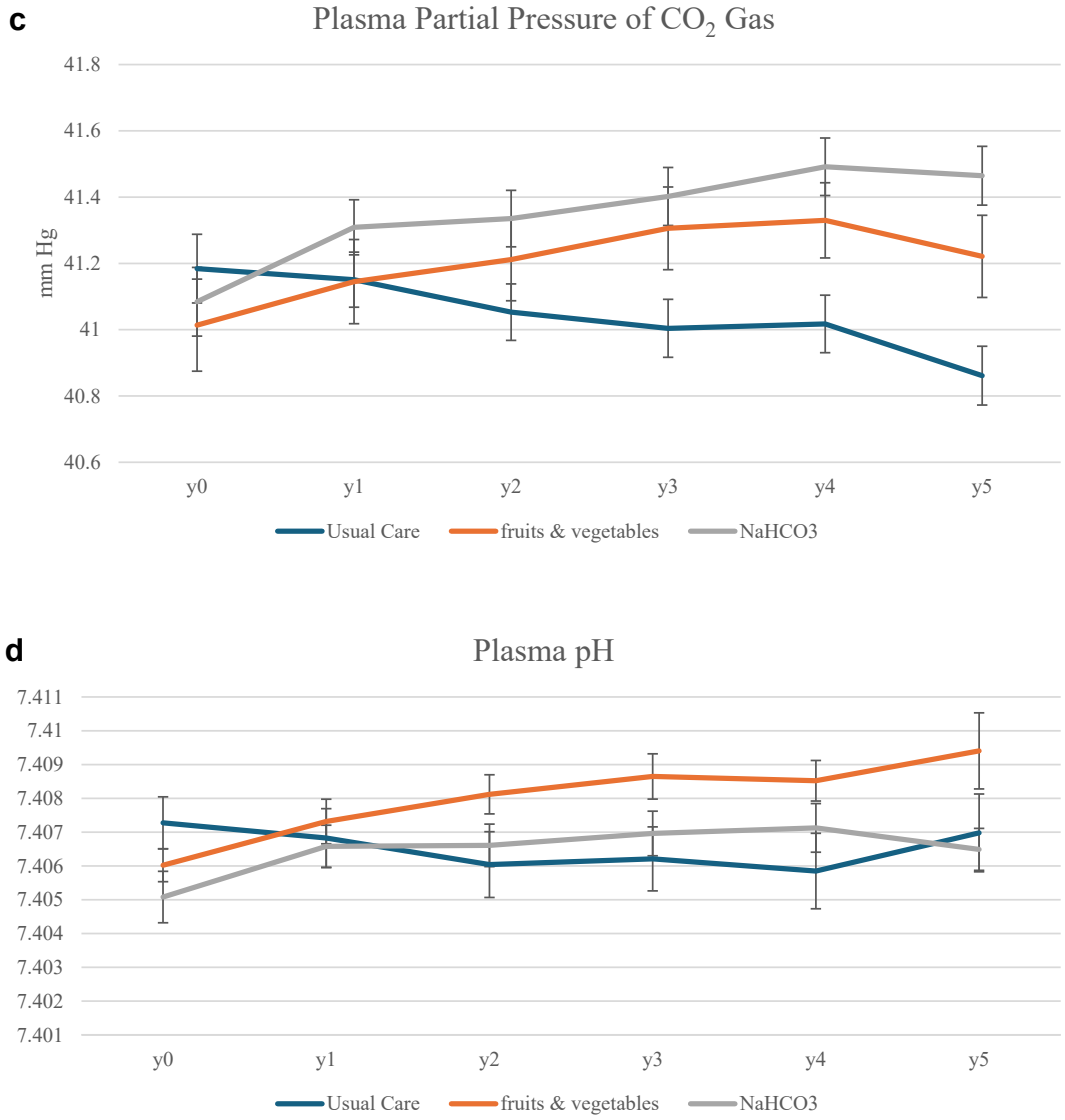

Figure 2. (Continued) (c) Plasma partial pressure of CO_2 gas (PCO_2, mm Hg); trajectories show a greater increase in plasma partial pressure CO_2 gas in participants given fruits and vegetables or $NaHCO_3$ than those receiving Usual Care, evident in year 2 and later relative to baseline. (d) Plasma pH (PpH); there were no consistent trajectory differences for PpH among the 3 groups. Usual Care participants received standard care without additional dietary acid reduction; fruits and vegetables participants received these foods to reduce dietary acid production by half; $NaHCO_3$ participants received oral sodium bicarbonate ($NaHCO_3$) as dietary acid reduction at 0.4 mEq/kg bw/d to match the alkali content of the fruit and vegetable provision; x-axis points indicate year of follow-up.

distribution, assumed to be 50% of body weight.[59] We assumed that "unaccounted HCO_3^-", that is, the difference between expected and observed $PTCO_2$ in response to the orally administered $NaHCO_3$, was HCO_3^- that had been titrated by accumulated acid. Retained HCO_3^- was $NaHCO_3$ dose minus urine HCO_3^- excretion for the time-period. Acid accumulation was determined by measuring 2-hour urine net acid excretion (UNAE) and venous $PTCO_2$ in the 3 CKD groups after an oral 0.5 mEq/kg lean bw $NaHCO_3$ bolus as detailed previously[60]:

Acid accumulation = ([retained HCO_3^-/0.5 × body wt] − observed increase in plasma HCO_3^-] × 0.5 body weight.

This strategy was designed to assess the amount of body acid present, including accounting for tissue buffering, as opposed to measures of only tissue pH[61] which assesses "free" acid but does not account for acid buffered by tissue. Tissue acid accumulation increases oxidative stress[62] and angiotensin II receptor activity[63] and so might contribute to kidney injury.[54,55]

Personnel performing the analyses were unaware of the group assignment of the participant samples.

Our local institutional review board approved the study protocols. The analytic plan is described in the Supplementary Methods.

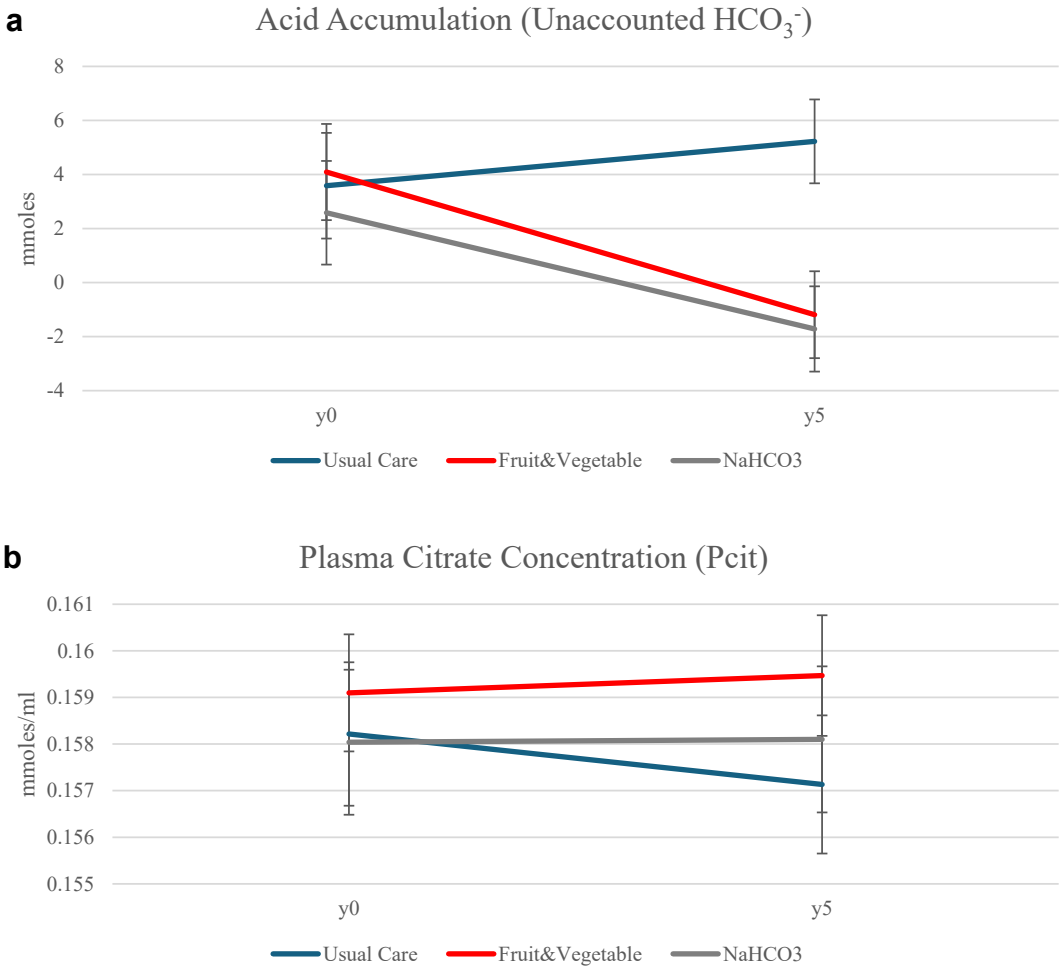

Figure 3. Trajectories for the 3 intervention groups regarding assessments of systemic acid-base status not routinely measured in clinical settings. The trajectories include cell means and standard errors measured at baseline the at year 5 of the intervention. (a) Acid accumulation assessed as unaccounted HCO_3^- (mmol); acid accumulation increased in those receiving Usual Care but decreased in those given fruits and vegetables and $NaHCO_3$ relative to baseline. Acid accumulation was not different between the 2 intervention groups. (b) Plasma citrate concentration (Pcit, mmol/ml); changes in plasma citrate concentration failed Bonferroni correction. (Continued)

RESULTS

In Figure 1, we show the CONSORT diagram. In Table 1, we show demographic characteristics and baseline clinical measures. Distribution of sex, race/ethnicity, or age were not different among groups at baseline. There were no differences among the groups in baseline values for PRAL, systolic blood pressure, eGFR, and serum electrolytes. To serve as a manipulation check, we examined whether groups differed with respect to changes in PRAL from year 1 through year 5 relative to baseline. Those analyses indicated that F&V showed a significant decrease in PRAL ($P < 0.001$) relative to baseline, whereas UC and HCO_3 groups did not ($P > 0.354$), based on mixed linear regressions with random person intercepts.

In Table 2, we show the descriptive statistics on all measures for the groups. Tables 3 and 4 show *P*-values associated with the interaction terms of group by time indicators for acid-base and kidney-related outcomes, respectively. Each *P*-value in Tables 3 and 4 reflects a period of net change (e.g., "year 5-Base" means the change from baseline to year 5) for the contrasted groups (e.g., UC vs. F&V) for each outcome. Hence, significant p-values indicate when group differences first emerged and whether they were sustained over the assessment schedule of that outcome. Tables also show lower and upper limits of the 95% confidence intervals for the net changes in each arm from baseline to year-5. To gauge strength of trends over time within groups, line graphs are shown in Figures 2 to 4 (acid-base) and Figure 5 (kidney outcomes) depicting cell means and standard errors for all outcomes.

Acid Accumulation

The interaction terms in Table 3 for plasma acid-base parameters commonly assessed by clinicians; $PTCO_2$, $[HCO_3^-]$ ($PHCO_3^-$), and PCO_2, assessed annually,

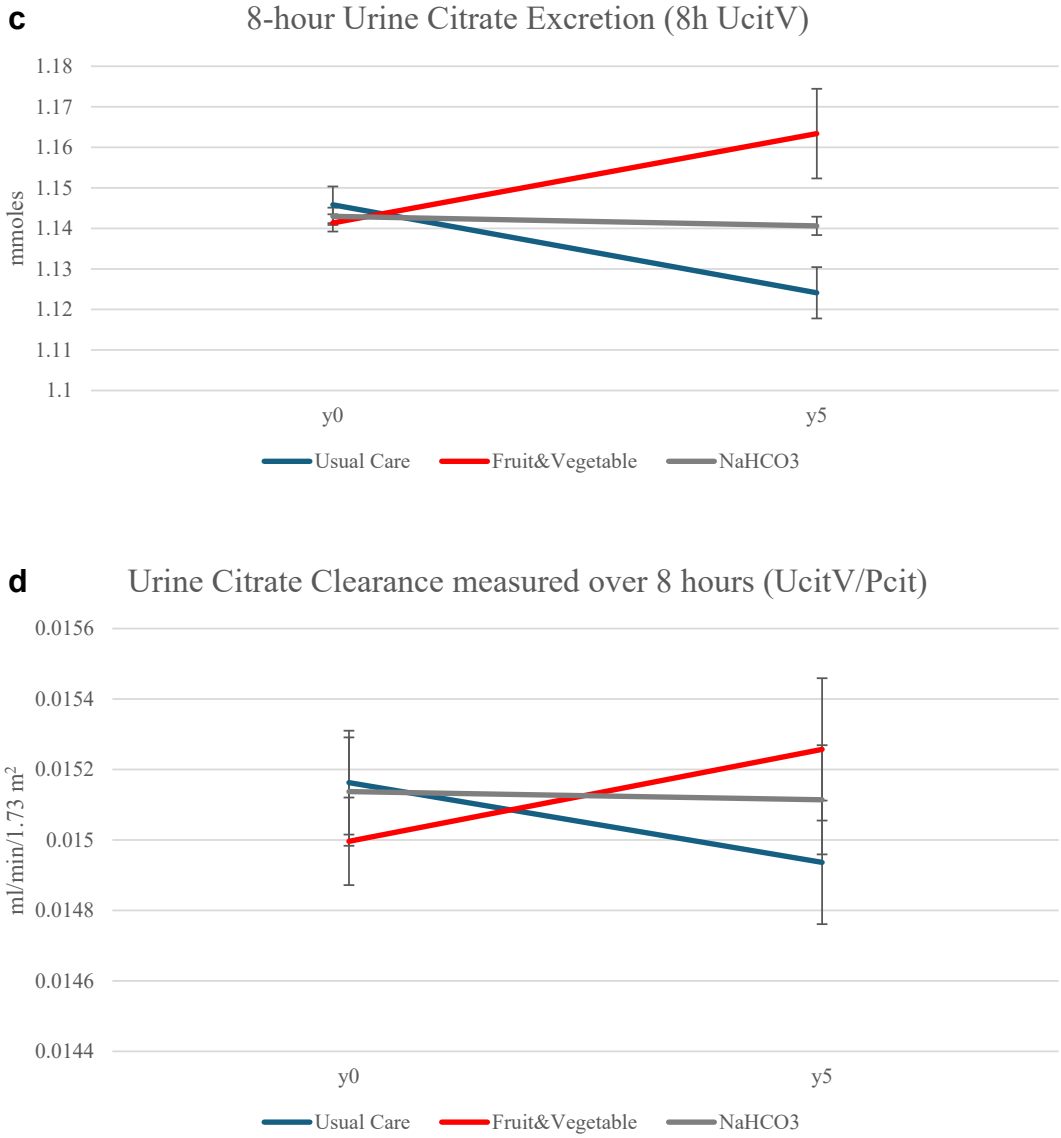

Figure 3. (Continued) (c) Eight-hour urine citrate excretion (8h UcitV, mmol); urine citrate excretion at 5 years was lower in Usual Care than in those given fruits and vegetables or $NaHCO_3$ and was higher in those given fruits and vegetables than $NaHCO_3$ relative to baseline. (d) Urine citrate clearance (UcitV/Pcit, ml/min per 1.73 m^2) measured over 8 hours; changes were larger for those given fruits and vegetables than those receiving Usual Care or $NaHCO_3$. Usual Care participants received standard care without additional dietary acid reduction; fruits and vegetables participants received these foods to reduce dietary acid production by half; $NaHCO_3$ participants received oral sodium bicarbonate ($NaHCO_3$) as dietary acid reduction at 0.4 mEq/kg bw/d to match the alkali content of the fruit and vegetable provision; x-axis points indicate year of follow-up.

indicate higher values in F&V and HCO_3^- than in UC, emerged in year-2, and were sustained thereafter. There were no significant differences between the 2 intervention groups. These trajectory differences emerged earlier in year 1 between the HCO_3^- and UC groups for $PHCO_3^-$ and PCO_2 (Table 3). For plasma pH, the pattern of changes across groups was less clear. For example, changes from baseline to year 4 but not year 5 were significant between UC and HCO_3^-, and the change from baseline to year 5 became significant between F&V and HCO_3^- groups. Figure 2a to d show the trajectories.

We also collected measures of overall systemic acid-base status that are not commonly assessed by clinicians. These measures included acid accumulation, citrate homeostasis, and urine acid-base excretion, at baseline and in year 5 (Table 3) to better understand effect(s) of the 2 interventions. Interaction terms for acid accumulation (Figure 3a) indicated that the net changes from baseline to year 5 for F&V and HCO_3^- were significantly different from corresponding changes in UC, consistent with lower acid accumulation in intervention groups than UC. There were no differences between the 2 intervention

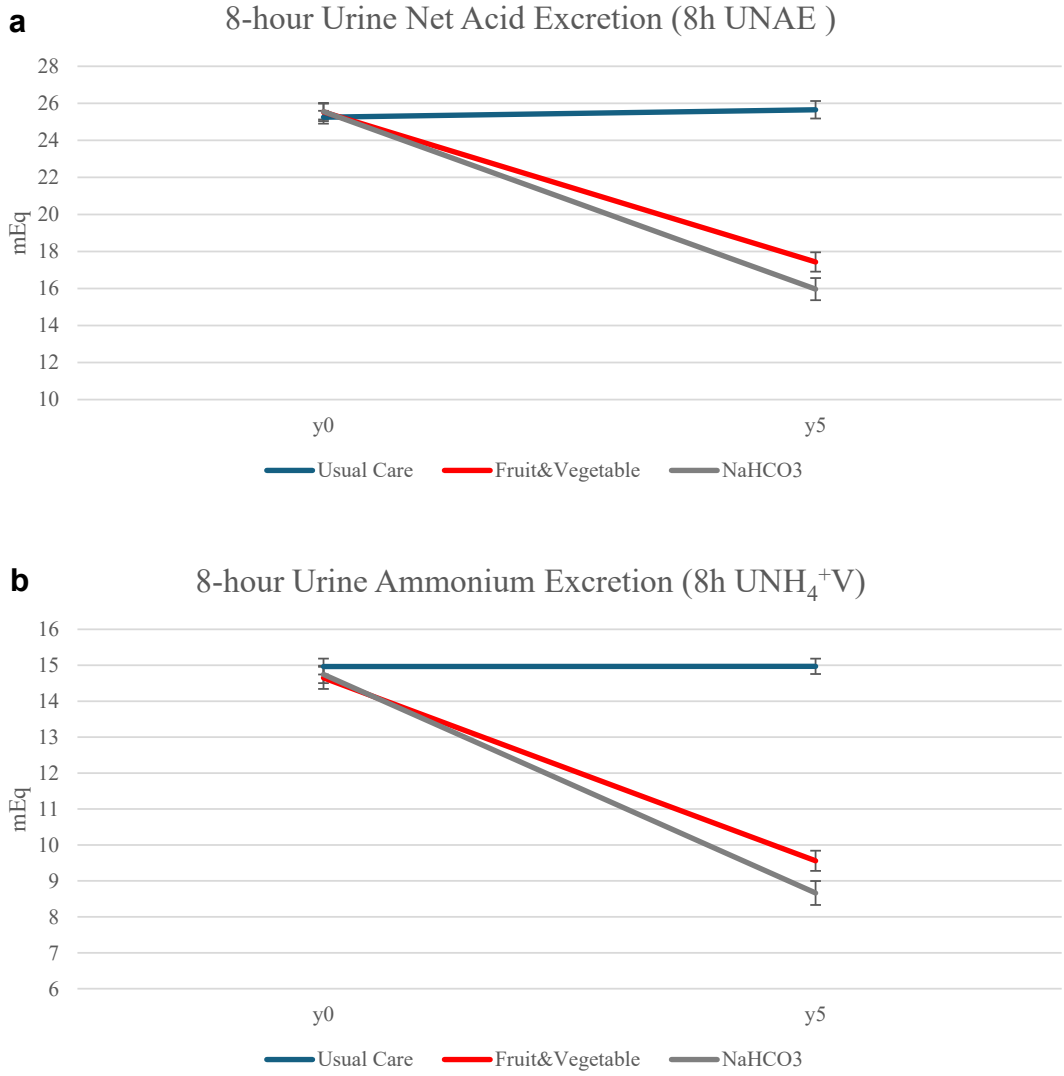

Figure 4. Trajectories for the 3 intervention groups regarding urine excretion of acid-base parameters. The trajectories include cell means and standard errors measured at baseline then at year 5 of the intervention. (a) Eight-hour urine net acid excretion (8 h UNAE, mEq); 8-hour UNAE excretion change was greater in those given fruits and vegetables or $NaHCO_3$ groups than those receiving Usual Care and was greater in those receiving $NaHCO_3$ than fruits and vegetables. (b) Eight-hour urine ammonium excretion (8-hour UNH_4^+V, mEq); 8-hour UNH_4^+V excretion change was greater in those given fruits and vegetables or $NaHCO_3$ than those receiving Usual Care and was greater in those given $NaHCO_3$ than fruits and vegetables. (Continued)

groups. Findings for measures of citrate homeostasis are in Figure 3b to d. Interaction terms for 8-hour urine citrate excretion (8-hour UcitV, Figure 3c) indicated that changes from baseline to year 5 for F&V and HCO_3 were significantly different and more positive from corresponding changes in UC. The F&V compared to the HCO_3^- group showed larger 8-hour UcitV changes. Findings for urine citrate clearance (UcitV/plasma citrate concentration, Figure 3d) indicated that changes from baseline to year 5 were larger for F&V than for UC and HCO_3^-. Nevertheless, despite statistical similarity at baseline UcitV/plasma citrate concentration, these measures showed large variability, reducing confidence in the pattern of changes, especially between UC and HCO_3^-. We did not interpret interaction effects for plasma citrate concentration (Figure 3b) because this measure failed the first omnibus Bonferroni correction. Interaction terms for 8-hour urine parameters, overall acid-base excretion (8-hour UNAE) and excretion of ammonium (8-hour UNH_4^+V), titratable acid (8-hour UTAV), and bicarbonate (8-hour $UHCO_3^-V$) for F&V and HCO_3^- in Table 3 were significantly different from corresponding changes in UC. Net changes between F&V and HCO_3^- were significant for UNAE, UNH_4^+V, and UTAV, but not for $UHCO_3^-V$. Trajectories for these urine acid-base changes are in Figure 4a to d.

Kidney Outcomes

The interaction terms in Table 4 for outcomes related to kidney injury, that is, UACR, urine N-acetyl-β-D-

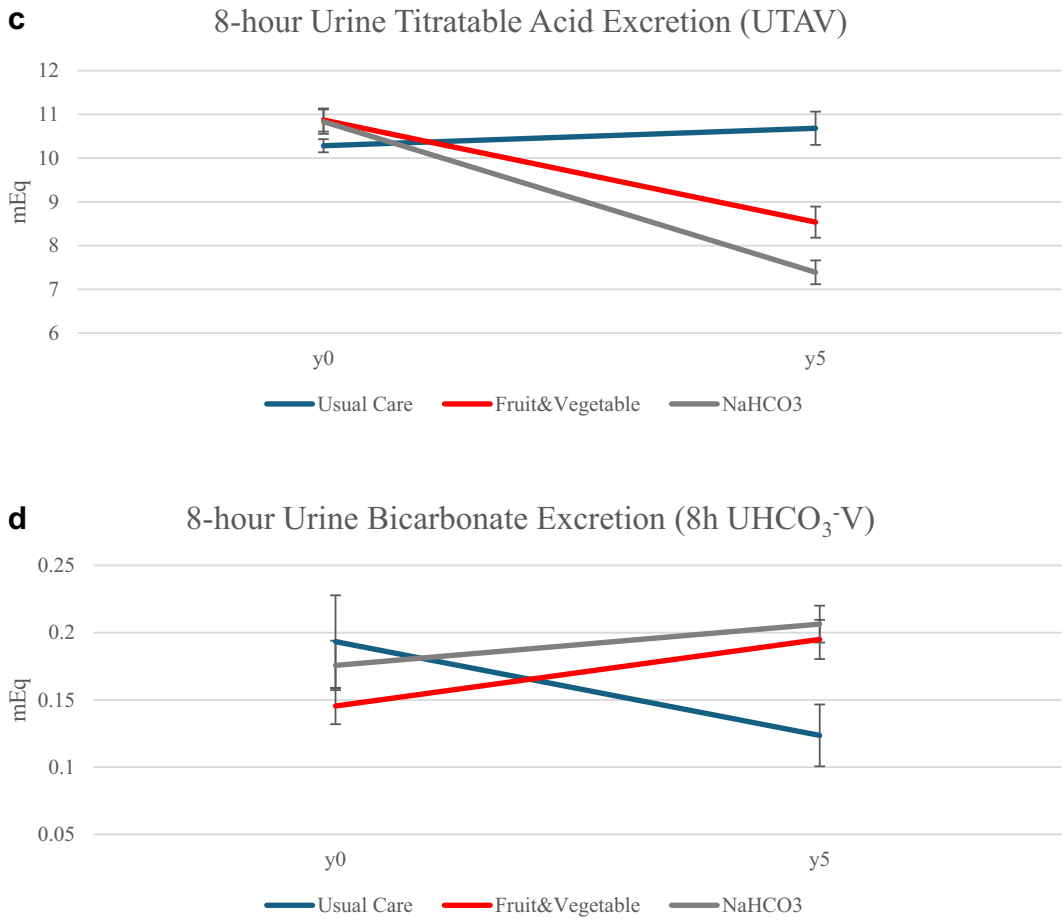

Figure 4. (Continued) (c) Eight-hour urine titratable acid excretion (8-hour UTAV, mEq); 8-hour UTAV excretion change was greater in those receiving fruits and vegetables or $NaHCO_3$ than those receiving Usual Care and was greater in those given $NaHCO_3$ than fruits and vegetables. (d) Eight-hour urine bicarbonate excretion (8-h $UHCO_3^-V$, mEq); 8-hour $UHCO_3^-V$ excretion change was greater in those receiving fruits and vegetables or $NaHCO_3$ than those receiving Usual Care but was not different between those given $NaHCO_3$ or fruits and vegetables. Usual Care participants received standard care without additional dietary acid reduction; fruits and vegetables participants received these foods to reduced dietary acid production by half; $NaHCO_3$ participants received oral sodium bicarbonate ($NaHCO_3$) as dietary acid reduction at 0.4 mEq/kg bw/d to match the alkali content of the fruit and vegetable provision; x-axis points indicate year of follow-up.

glucosamine-to-creatinine ratio (in units/g), urine angiotensinogen-to-creatinine ratio (in μg/g), and urine 8-iso prostaglandin F2α–to-creatinine ratio (U8-iso, in μg/g), indicate significant net improvements were evident in year 2 in F&V and HCO_3^- than UC; there were no significant differences between the 2 intervention groups. These differences emerged earlier in year 1 for urine angiotensinogen and UACR between the HCO_3^- and the UC groups. Figure 5a to d show the trajectories for these outcomes. These differences were copresent with faster eGFR decline in UC than the 2 intervention groups as presented in a recent publication,[64] and in year 5 eGFR that was higher in F&V, (mean [SD] = 96.5 [5.4]) and HCO_3^- (95.9 [6.6]) than in UC (92.1 [8.1]) ml/min per 1.73 m^2, $P < 0.001$]. Trajectories for eGFR, UACR, systolic blood pressure, low-density lipoprotein , and body mass index are presented in the Supplementary Figures S1 to S5.

DISCUSSION

In this randomized, interventional 3-arm trial of participants with macroalbuminuric, primary hypertension-associated CKD and normal eGFR, dietary acid reduction over 5 years with either F&Vs or $NaHCO_3$ (HCO_3^-) yielded improved (i.e., less acid) systemic acid-base status. Improvement was manifest by parameters not usually assessed clinically, including less acid accumulation and greater urine citrate excretion (8-hour UcitV). Improved acid-base status was also manifest by parameters assessed clinically, including higher levels of $PTCO_2$, $PHCO_3^-$, and PCO_2. The 2 intervention groups had lower UNAE excretion than UC, consistent with a reduced acid challenge. Furthermore, improved acid-base status was associated with less oxidative stress assessed by lower U8-iso excretion, and less kidney injury assessed by lower UACR, urine N-acetyl-β-D-glucosamine, and urine angiotensinogen excretion. Indeed, both intervention

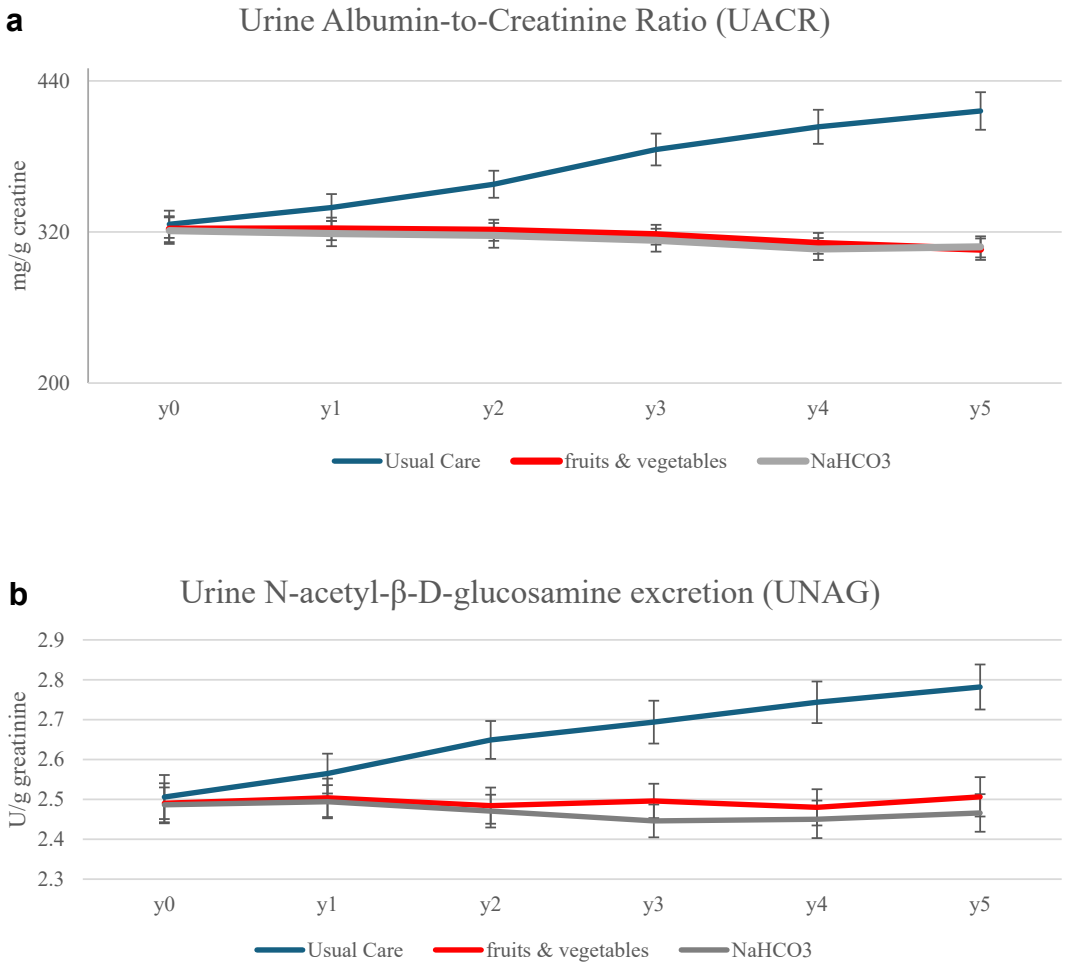

Figure 5. Trajectories for the 3 intervention groups regarding kidney related parameters. The trajectories include cell means and standard errors measured at baseline then at year 5 of the intervention. (a) Urine albumin-to-creatinine ratio (UACR, in mg/g); trajectories for UACR were lower than Usual Care for those given fruits and vegetables or $NaHCO_3$ beginning in year-2 and later relative to baseline; there were no differences between those given fruits and vegetables or $NaHCO_3$. (b) Urine N-acetyl-β-D-glucosamine-to-creatinine ratio (UNAG, in units/g); Trajectories for UNAG were lower than Usual Care for those given fruits and vegetables or $NaHCO_3$ beginning in year-2 and later relative to baseline; there were no differences between those given fruits and vegetables or $NaHCO_3$. (Continued)

groups had higher eGFR at 5 years than UC. These data show that typical modern diets, largely acid-producing,[4] can cause sustained acid accumulation in those with normal eGFR, similar to patients with CKD and reduced eGFR. In addition, this acid accumulation can be reduced by less acid-producing foods or by mineral alkali like $NaHCO_3$; both interventions were associated with less kidney injury.

This 5-year trial in participants eating their baseline, acid-producing diets while remaining in their lived environments, complements earlier short-term studies in participants given acid-producing mineral salts while housed in research facilities. This trial showing internally assessed acid accumulation also complements these earlier studies showing acid accumulation through external balance studies (acid out < acid produced),[22–24] each in participants with normal eGFR. That different experimental approaches conducted in different settings yield the same conclusion strongly supports that, modern acid-producing diets can cause acid accumulation in patients with CKD and normal kidney function.

This trial supports that normal eGFR in patients with CKD does not guarantee against sustained acid accumulation when eating modern acid-producing diets. Similarly, animals with normal nephron mass given acid-producing mineral salts in their chow had sustained acid accumulation while in net acid balance (i.e., dietary acid intake = urine acid excretion).[65] This acid accumulation in animals with normal nephron mass eating acid-producing chow was greater than in those eating non-acid-producing chow.[66,67] Furthermore, acid accumulation in animals with normal nephron mass was less than in animals with two-thirds nephrectomy (2/3 Nx) when both ate acid-producing diets.[66] Despite greater acid accumulation in 2/3 Nx, both 2/3 Nx and normal nephron mass animals were in net acid balance with $PTCO_2$ only slightly but not significantly lower in 2/3 Nx.[67] Both 2/3 Nx and normal

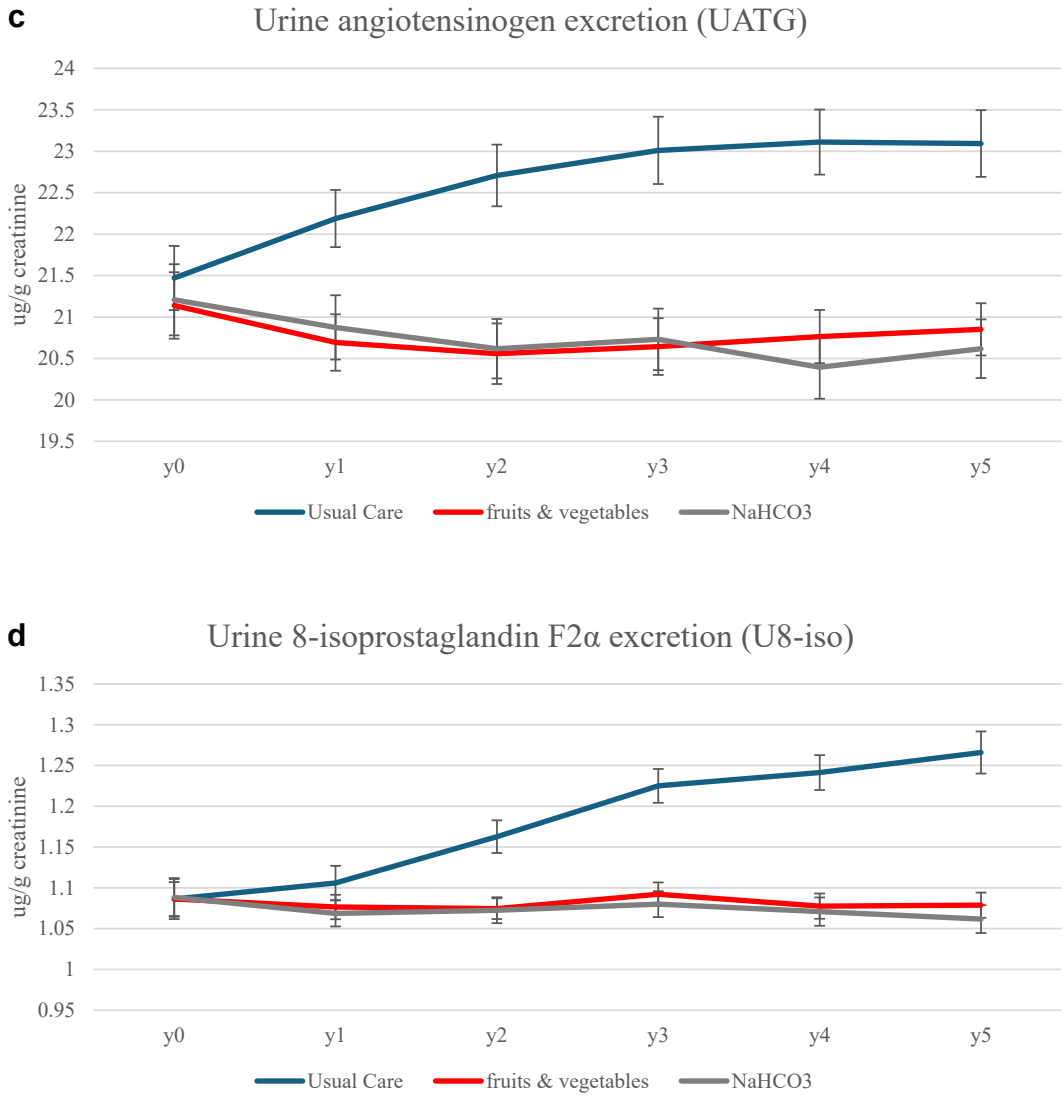

Figure 5. (Continued) (c) Urine angiotensinogen excretion-to-creatinine ratio (UATG, in μg/g); trajectories for UATG were lower than Usual Care for those given fruits and vegetables or $NaHCO_3$ and were no different between those given fruits and vegetables or $NaHCO_3$. (d) Urine 8-isoprostaglandin F2α–to-creatinine (U8iso, in μg/g); trajectories for UATG were lower than Usual Care for those given fruits and vegetables or $NaHCO_3$ beginning in year-2 and later relative to baseline; there were no differences between those given fruits and vegetables or $NaHCO_3$. Usual Care participants received standard care without additional dietary acid reduction; fruits and vegetables participants received these foods to reduced dietary acid production by half; $NaHCO_3$ participants received oral sodium bicarbonate ($NaHCO_3$) as dietary acid reduction at 0.4 mEq/kg bw/d to match the alkali content of the fruit and vegetable provision; x-axis points indicate year of follow-up.

nephron mass animals returned to baseline, and not significantly different, levels of acid accumulation, only after they stopped eating the acid-producing diet.[67] This 5-year trial showing that dietary acid reduction in study participants with normal eGFR lowers acid accumulation is concordant with these animal studies.

This trial not only supports that modern acid-producing diets can cause acid accumulation in patients with normal eGFR but can also threaten kidney health. Clinicians are unlikely to identify the significant acid accumulation in UC compared to F&V and HCO_3^- groups by assessing the minor reductions in $PTCO_2$, $PHCO_3^-$, and PCO_2. In contrast, quantitatively greater changes in 8-hour UcitV might have clinical utility to do so, as suggested by earlier studies.[15-17] Ongoing research will determine the clinical utility of UcitV, particularly that assessed with a "spot"[68] rather than a timed[15-17] urine sample. Relatedly, this trial suggests that identifying high dietary acid intake in patients with primary hypertension and CKD is clinically important. Assessing the acid-producing capacity of diets can be done by tabulating foods eaten[69] and assigning their acid- or base-producing capacity,[4] however, this is labor-intensive, of questionable accuracy,[70] and is not clinically practical. This trial shows that participants undergoing dietary acid reduction had lower UNH_4^+V than UC; earlier studies showed

that UNH_4^+V associated directly with the level of dietary acid production in participants with primary hypertension and normal kidney function.[17] This trial and the earlier studies support that UNH_4^+V should be further explored as a potential indicator of dietary acid production. Currently, clinical laboratories do not measure urine NH_4^+, however, because of its potential importance in assessing patient acid-base status, its measurement might soon become more practical.[71]

Here, we show that both F&V and $NaHCO_3$ interventions yielded similar kidney protection compared to UC. Together with earlier evidence, however, F&V might be the preferred dietary acid reduction strategy in patients with CKD associated with primary hypertension. Diets high in F&Vs are already recommended first-line treatments for patients with primary hypertension[72] and CKD.[73] In addition, diets high in F&Vs are associated with lower risk for, and progression of, CKD,[74,75] improved indices of CVD risk,[76] and lower CVD mortality.[76,77] Furthermore, dietary sodium was associated with decreased kidney[78] and cardiovascular[78,79] protective effects of anti–angiotensin II therapy, a mainstay treatment of patients with albuminuric CKD.[73] These data support F&V rather than $NaHCO_3$ as the preferred strategy for dietary acid reduction in patients with primary hypertension and CKD. Whether the F&V intervention provides additive kidney and/or cardiovascular protection to modern drug therapies such as sodium glucose cotransport type 2 inhibition awaits testing. One challenge to this approach is that F&V intake in the USA is generally low[80] and is even lower in those with CKD.[81] Overcoming this challenge calls for a greater clinical focus on dietary management of CKD, including greater focus on F&Vs, particularly in its earlier stages.[82]

Limitations of this study include no specific data on compliance with the $NaHCO_3$ prescription or the F&V provision, although all participants in the intervention groups had comparable decreases in UNAE, which is consistent comparable alkali intake.[29] We did not test participants with normoalbuminuria to examine if the macroalbuminuria in all study participants influenced the described acid-base responses. In addition, the method used to measure creatinine at the time these studies began is no longer standard.

In conclusion, this trial showed that dietary acid reduction with either F&V or $NaHCO_3$ in participants with macroalbuminuric CKD and normal eGFR yielded a less acid systemic acid-base status and provided similar kidney protection. The trial shows that acid-producing modern diets cause sustained acid accumulation even in patients with CKD and normal eGFR and support that such diets threaten kidney health. These studies support dietary acid reduction, preferably with F&Vs, for kidney protection in patients with primary hypertension and macroalbuminuric CKD.

DISCLOSURE

MK reports foundation grant support, travel support to attending scientific meetings, support as a member of Advisory Boards, and stock options in some for-profit companies. NA reports foundation grant support. DEW reports Honoria for scientific presentations. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

Data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DEW conceived, designed, and oversaw conduct of the research. NG and NEM contributed additional design suggestions, additional parameters to measure, and additional analyses. MK contributed additional suggested analyses. NA conducted the statistical analyses. JS conducted analyses of body fluid parameters. DEW, NG, NEM, MK, NA, and JS interpreted results of experiments. DEW, NG, NEM, MK, and NA analyzed the data. NA prepared the tables and figures. DEW wrote the original manuscript draft. DEW, NG, NEM, MK, NA, and JS edited and revised the manuscript. DEW, NG, NEM, MK, NA, and JS approved final version of manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Analytic Plan.

Study Protocol.

Supplementary Reference.

Figure S1. Estimated glomerular filtration rate. Trajectories show less estimated glomerular filtration rate decline in participants given fruits and vegetables or oral NaHCO3 than those receiving usual care.

Figure S2. Urine-albumin-to-creatinine ratio (in mg/g). Trajectories show less urine albumin-to-creatinine ratio increase in participants given fruits and vegetables or oral NaHCO3 than those receiving usual care.

Figure S3. Systolic blood pressure. Trajectories show greater systolic blood pressure decline in participants given fruits and vegetables than those given oral NaHCO3 or receiving usual care.

Figure S4. Plasma low density lipoprotein cholesterol (LDL). Trajectories showed greater relative reductions in LDL cholesterol in participants given fruits and vegetables than those given oral NaHCO3 or receiving usual care that was evident in year 2.

Figure S5. Body mass index. Trajectories showed greater relative reductions in body mass index in participants given fruits and vegetables than those given oral NaHCO3 or receiving usual care that was evident in year 1.

CONSORT Checklist.

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