This was a 1-year, single-center, prospective, randomized, interventional study in 71 subjects with Stage 4 CKD (eGFR 15 – 29 mL/min/1.73m²) due to hypertensive nephropathy and plasma total CO2 < 22 mM. The objective of the study was to compare the effect of dietary fruits and vegetables vs. oral sodium bicarbonate on eGFR, metabolic acidosis and markers of kidney injury.

The primary outcome measure was the change in cysGFR and crGFR in response to 1 year of dietary fruits and vegetables or oral sodium bicarbonate. Secondary outcomes were the change from baseline to end of treatment in plasma and urine acid-base measures, urine excretion of cystatin C and creatinine, systolic blood pressure, body weight, urine measures of kidney injury (urine albumin, NAG, TGF-β) plasma potassium and urine potassium excretion, and determinants of urine potassium excretion (plasma and urine aldosterone and 11β-hydroxysteroid dehydrogenase type 2 activity as assessed as urine THF/THE ratio).

After participation in a 6-month blood pressure reduction program, eligible subjects were randomized into one of two treatment groups:

- Oral sodium bicarbonate tablets (1.0 mEq/kg ideal body weight per day; 35 subjects), or
- Fruits/vegetables in amounts to reduce dietary potential renal acid load by 50% (36 subjects)

The two treatment groups were well matched for demographics and baseline characteristics; study subjects had mean crGFR and cysGFR values ~23 mL/min/1.73m² and ~21 mL/min/1.73m², respectively, and mean venous total CO2 levels ~19 mM. Baseline characteristics of the study population are presented in Table 1.
At the end of the 1-year treatment period, metabolic acidosis, as measured by an increase in plasma total CO2 levels, was significantly improved in both the sodium bicarbonate and fruits/vegetables treatment groups (p<0.01). Plasma total CO2 was significantly higher after 1 year in the patients receiving oral sodium bicarbonate (21.1 ± 1.3 mM) compared to those receiving fruits/vegetables (19.9 ± 1.7 mM) (p<0.01) (Figure 1). Similarly, 8-hour net acid excretion was significantly lower in both treatment groups (p<0.01), with a larger effect observed in the oral sodium bicarbonate group compared to the fruits/vegetables group (Figure 2).

Figure 1: Goraya, 2013 (originally Figure 2, left panel, in study)

Plasma total CO2 (TCO2) in patients with CKD stage 4, at baseline and 1-year follow-up. Bicarbonate recipients were given oral sodium bicarbonate at 1.0 mEq/kg lean body weight per day; the fruit and vegetable recipients were given fruits and vegetables in amounts designed to reduce potential renal acid load by half.

The white line through each box indicates the median plasma TCO2. The box represents the inner quartile range of the differences in plasma TCO2, or the 25 and 75% percentiles of the plasma TCO2 differences. The lines extending from the box indicate the range, or minimum and maximum, of the differences in plasma TCO2.
8-hour urine net acid excretion in patients with CKD stage 4, at baseline and 1-year follow-up. Bicarbonate recipients were given oral sodium bicarbonate at 1.0 mEq/kg lean body weight per day; the fruit and vegetable recipients were given fruits and vegetables in amounts designed to reduce potential renal acid load by half.

The white line through each box indicates the median 8h NAE. The box represents the inner quartile range of the differences in 8h NAE, or the 25 and 75% percentiles of the 8h NAE differences. The lines extending from the box indicate the range, or minimum and maximum, of the differences in 8h NAE.
Mean cysGFR and crGFR decreased slightly (< 2 mL/min), but significantly (p<0.05), from baseline to end-of-treatment in both treatment groups; the two treatment groups did not differ significantly from each other (Figure 3).

**Figure 3: Goraya, 2013 (originally Figure 4, left panel, in study)**

Bicarbonate recipients were given oral sodium bicarbonate at 1.0 mEq/kg lean body weight per day; the fruit and vegetable recipients were given fruits and vegetables in amounts designed to reduce potential renal acid load by half.

crGFR = glomerular filtration rate determined from plasma values of creatinine; cysGFR = glomerular filtration rate determined from plasma values of cystatin.

The white line through each box indicates the median GFR. The box represents the inner quartile range of the differences in GFR, or the 25 and 75% percentiles of the GFR differences. The lines extending from the box indicate the range, or minimum and maximum, of the differences in GFR.

* P < 0.05 vs respective baseline

**SOURCE:** Goraya, 2013
Treatment with oral sodium bicarbonate and fruits/vegetables both resulted in significant (p<0.01) decreases in three markers of kidney damage over the 1-year treatment period (Figure 4). Urine albumin was assessed as a marker of general kidney injury; urine NAG is an index of kidney tubulointerstitial injury and an index of kidney injury induced by dietary acid; and urine TGF-β has been shown to reflect kidney injury induced by dietary acid in an experimental CKD model and might be a mediator of hypertensive nephropathy.

**INDICES OF KIDNEY INJURY BEFORE & AFTER 1 YEAR OF TREATMENT**

![Box plots showing indices of kidney injury](source: Goraya, 2013)

Figure 4: Goraya, 2013 (originally Figure 5 in study)

Left panel: urine albumin (8h Ualb); middle panel: urine N-acetyl β-D-glucosaminidase (8h UNAG); right panel: urine TGF-β (8h UTGF). Bicarbonate recipients were given oral sodium bicarbonate at 1.0 mEq/kg lean body weight per day; the fruit and vegetable recipients were given fruits and vegetables in amounts designed to reduce potential renal acid load by half.

The white line through each box indicates the median indices of kidney injury. The box represents the inner quartile range of the differences in indices of kidney injury, or the 25 and 75% percentiles of the indices of kidney injury differences. The lines extending from the box indicate the range, or minimum and maximum, of the differences in indices of kidney injury.

After 1 year, mean plasma potassium was not significantly changed from baseline in the oral sodium bicarbonate group or the fruits/vegetables group. Mean 8-hour urine potassium excretion was higher at 1-year than at baseline in both groups (p<0.01), and was higher in the fruits/vegetables group than in the sodium bicarbonate group (p<0.01). Despite the increased dietary potassium load associated with the fruit/vegetable treatment, patients in this group did not become hyperkalemic. It is noted, however, that the enrollment criteria for this study excluded those at high risk for hyperkalemia.

At 1 year, 8-hour urine aldosterone excretion (an index of aldosterone secretory rate) increased compared with baseline in the fruits/vegetables group (p<0.001) and decreased compared with baseline in the sodium bicarbonate group (p<0.01) (Figure 5). The authors suggest that this higher urine aldosterone excretion might indicate greater distal nephron potassium secretion, particularly with non-chloride anions in the distal nephron lumen. The ratio of urine excretion of active cortisol (THF) to its inactive metabolite (THE) was not different between the two treatment groups at baseline, but at 1-year this ratio was increased in the fruits/vegetables group.
group (p<0.01) and decreased in the sodium bicarbonate group (p<0.01) (Figure 5). These data suggest that fruits and vegetables decreased 11β-hydroxysteroid dehydrogenase type 2 activity, allowing glucocorticoid access to the mineralocorticoid receptor with added stimulation of distal nephron potassium secretion.

**8-HOUR URINE ALDOSTERONE & CORTISOL METABOLITE EXCRETION**

Figure 5: Goraya, 2013 (originally Figure 6, left panel, in study)

Ratio of active (tetrahydrocortisol [THF]) to inactive (tetrahydrocortisone [THE]) urine cortisol metabolites in CKD stage 4 at baseline and 1-year follow-up. The THF/THE ratio indirectly assesses 11β-hydroxysteroid dehydrogenase enzyme activity that converts glucocorticoids to inactive metabolites. Higher ratios indicate lower activity.

Bicarbonate recipients were given oral sodium bicarbonate at 1.0 mEq/kg lean body weight per day; the fruit and vegetable recipients were given fruits and vegetables in amounts designed to reduce potential renal acid load by half.

The bottom and top of the boxes span the 25th and 75th percentile of data points. The white bar within the box indicates the 50th percentile or median. The whiskers indicate 1.5 times the interquartile range from the lower and upper quartiles.

Values for 8-hour urine sodium excretion and urine fractional sodium excretion were similar at baseline, but lower in the fruits/vegetables group than the sodium bicarbonate group at 1-year post-treatment.

Mean systolic blood pressure was lower after 1 year of treatment than at baseline in the fruits/vegetable group (131.7 ± 3.3 mmHg vs. 136.3 ± 4.8 mmHg; p<0.01), but not in the sodium bicarbonate treatment group (136.0 ± 4.4 mmHg vs. 136.1 ± 4.7 mmHg; p=0.84). Antihypertensive medication use was not significantly different between the two treatment groups. Mean body weight was also lower after 1 year of treatment than at baseline in the fruits/vegetable group (82.7 ± 6.1 kg vs. 78.0 ± 5.3 kg; p<0.01), but not in the sodium bicarbonate treatment group (84.3 ± 5.4 kg vs. 84.4 ± 5.0 kg; p=0.87). The lower mean systolic blood pressure observed in the fruits/vegetables treatment group may have resulted from reduced sodium intake (consistent with the observed lower urine sodium excretion), increased dietary potassium (consistent with decreased urine potassium excretion), and/or the observed weight loss associated with the lower calorie diet.
The authors concluded that this study demonstrated that treating metabolic acidosis in patients with Stage 4 CKD due to hypertensive nephropathy with fruits and vegetables or oral sodium bicarbonate is an effective kidney-protective adjunct to blood pressure control regimens including ACE inhibition. The limitations of this study are its relatively small size, its open-label design/the lack of a placebo-control and the use of only a single study site. A summary of the study design and results of the Goraya et al. (2013) study is presented in Table 2.

### Study Design and Results

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Texas Tech University Health Sciences Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria</td>
<td>Nonmalignant hypertension; eGFR 15 – 29 mL/min/1.73m²; plasma total CO₂ &lt; 22 mM; age ≥ 18 years; history of compliance with clinic visits; no diabetes or cardiovascular disease</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>Known primary kidney disease or findings consistent thereof; history of diabetes or fasting blood glucose ≥ 110 mg/dL; history of malignancy; chronic infection; pregnancy; clinical evidence of cardiovascular disease; peripheral edema or diagnoses associated with edema (i.e., heart failure); plasma potassium level &gt; 4.6 mEq/L; taking or inability to stop taking drugs (other than ACE inhibitors) that limit potassium excretion</td>
</tr>
<tr>
<td>Study Treatments</td>
<td>Oral sodium bicarbonate tablets (1.0 mEq/kg ideal body weight per day; 35 subjects) Fruits/vegetables in amounts to reduce dietary PRAL by 50% (36 subjects)</td>
</tr>
<tr>
<td>Randomization</td>
<td>After participation in a 6-month blood pressure reduction program, eligible subjects were randomized into the two treatment groups</td>
</tr>
<tr>
<td>Duration</td>
<td>1 year</td>
</tr>
<tr>
<td>Assessments</td>
<td>At baseline and end-of-treatment the following were assessed: systolic blood pressure; plasma and urine creatinine, aldosterone and cystatin C; venous plasma acid-base variables; urine 8-hour net acid excretion, albumin, N-acetyl-β-D-glucosaminidase (NAG) and transforming growth factor β (TGF-β). 8-hour urine excretion of cystatin C, creatinine, aldosterone, tetrahydrocortisol (THF), tetrahydrocortisone (THE), sodium and potassium were also determined.</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Cystatin C-estimated GFR (cysGFR) and creatinine-estimated GFR (crGFR) in response to 1 year of oral fruits and vegetables or sodium bicarbonate</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Plasma and urine acid-base measures, urine excretion of cystatin C and creatinine, systolic blood pressure, body weight, urine measures of kidney injury (urine albumin, NAG, TGF-β) plasma potassium and urine potassium excretion, and determinants of urine potassium excretion (plasma and urine aldosterone and 11β-hydroxysteroid dehydrogenase type 2 activity as assessed as urine THF/THE ratio)</td>
</tr>
<tr>
<td>Results</td>
<td>At the end of the 1-year treatment period: 1. Slower decline in kidney function as measured by eGFR as compared to those receiving placebo or sodium chloride 2. Significant decreases in urine ET-1 excretion, where this parameter increased or remained at baseline level in the two control groups. 3. A slower trajectory of urine NAG. 4. Relatively stable urine albumin, compared to increased values in two control groups. 5. Lower urine 8-hour net acid excretion, which was significantly lower than the values observed in the two control groups. 6. Higher urine potassium levels, which was significantly lower than the values observed in the two control groups. 7. No change in urine sodium or total venous CO₂. 8. Lower systolic blood pressure, as a result of treatment with ACE inhibitors, that was not different than in the two control groups.</td>
</tr>
</tbody>
</table>

Table 2: A Comparison of Treating Metabolic Acidosis in CKD Stage 4 Hypertensive Kidney Disease with Fruits and Vegetables or Sodium Bicarbonate (Goraya et al., 2013) CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; PRAL = potential renal acid load; ACE = angiotensin converting enzyme