

## **Metabolic Acidosis and Chronic Kidney Disease**

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### **Acidosis and Malnutrition**

- Anorexia
- Inhibition of albumin synthesis
- Protein degradation through ATP-Ubiquitin-proteasome pathway
- Oxidation of branched amino acids
- Correction of acidosis improves nutritional status in ESRD

## Acidosis and Progression of CRF

- Experimental CRF is associated with increased tubular ammonia production.
- Ammonia activates complement C3, alternative complement cascade and promotes tubulo interstitial fibrosis.
- Bicarbonate supplement interrupts above mechanism and prevent tubulo interstitial fibrosis

*Nath KA et al J Clin Invest 1985: 76; 667*

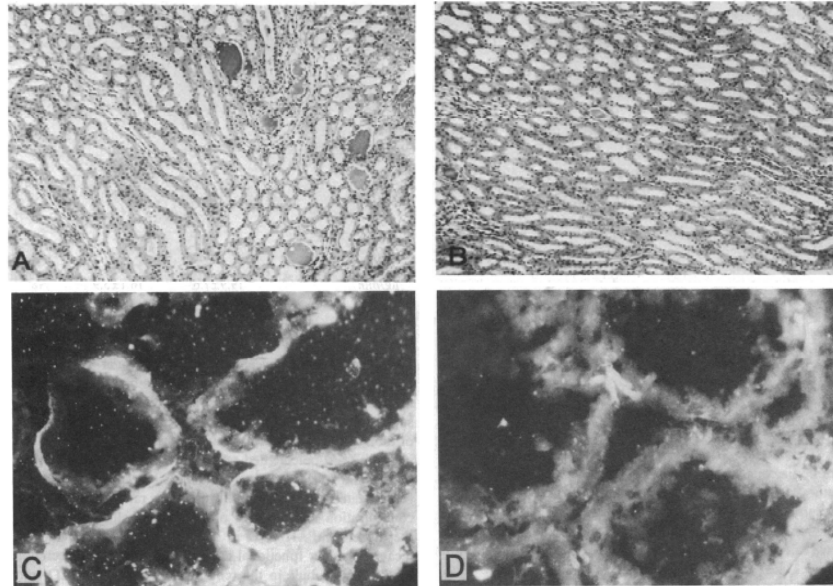
### **Pathophysiology of Chronic Tubulo-Interstitial Disease in Rats**

#### **Interactions of Dietary Acid Load, Ammonia, and Complement Component C3**

**K. A. Nath, M. K. Hostetter, and T. H. Hostetter**

*J. Clin. Invest. Volume 76, August 1985, 667-675*

*Departments of Medicine and Pediatrics, School of Medicine, University of Minnesota, Minneapolis, Minnesota 55455*

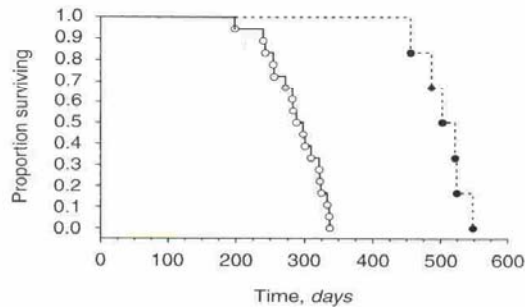
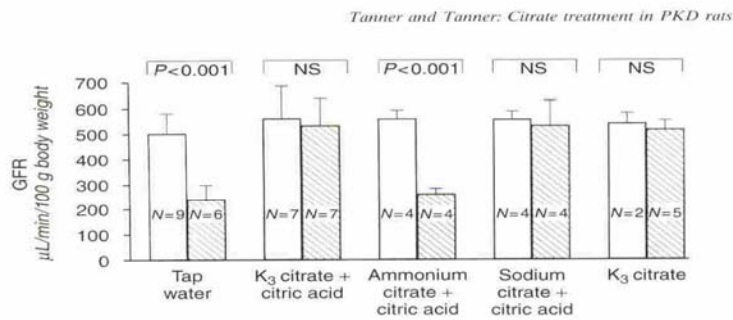
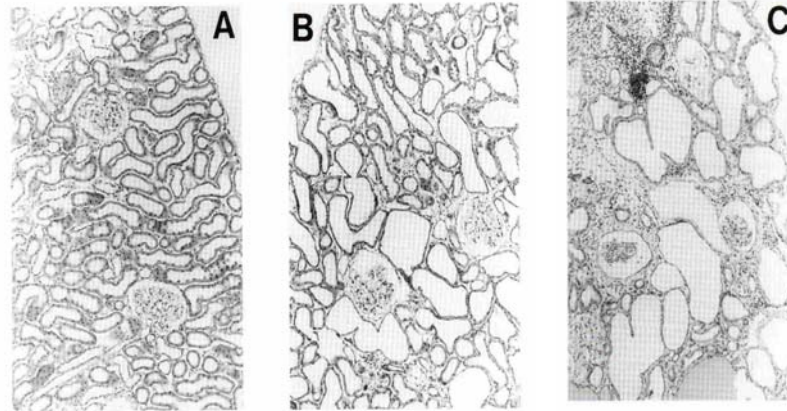


# Citrate therapy for polycystic kidney disease in rats

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*Kidney International*, Vol. 58 (2000), pp. 1859–1869



## Acidosis and Progression of CRF

- Metabolic acidosis does not contribute to chronic renal injury in the rat.

*Clin Sci 1995; 89: 643-65*

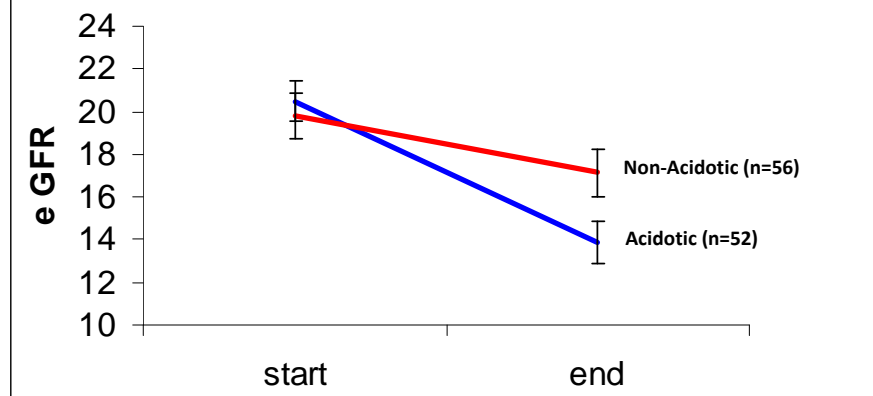
- Metabolic acidosis induces endothelin and promotes progression of renal failure in rats.

*Kidney Int. 2008; 73: 192-199*

- Tubular peptide hypermetabolism and urinary ammonia in CRF in man: A maladaptive response ?

*Nephron 1998; 79: 306-11*

**eGFR decline over 2-yrs  
Acidotic vs Non-Acidotic Patients**



**Aims:**

Effect of correction of acidosis in patients with CKD stage 4/5 on the rate of decline of eGFR, development of ESRD and nutritional status.

**Study Design:**

Open label prospective randomised control trial with two years follow up.

**Location:**

Pre dialysis clinic, Royal London Hospital, London, UK.

**Study Population:**

Patients aged 18-75 years with CKD stage 4/5 and mild metabolic acidosis ( $\text{HCO}_3^- < 21$  and  $> 16$  mmol/l).

**Exclusion Criteria:**

Chronic sepsis, uncontrolled HTN, Fluid overload/ CHF, Steroid therapy, Morbid obesity, Cognitive impairment.

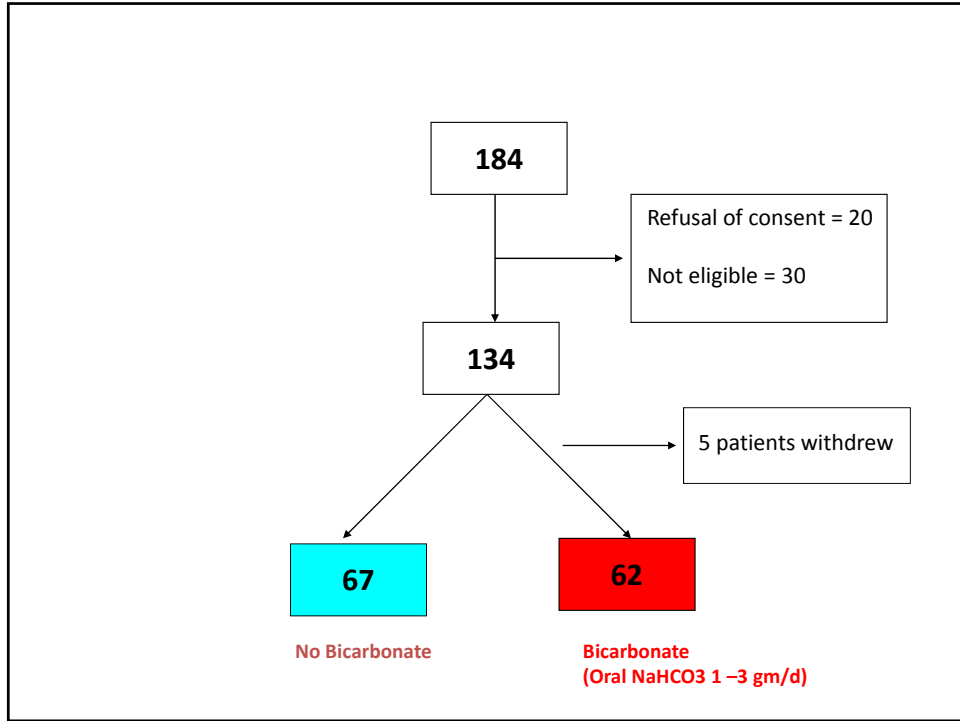
## Study Parameters

**Serial Assessment of Progressive CRF:**

Clinic Blood Pressure and any changes in anti hypertensive drugs  
Routine plasma biochemistry  
Creatinine clearance on 24 hr urine sample  
Urinary Protein, Sodium, Urea excretion on 24 hour urine sample

**Serial Assessment of Nutritional status:**

Weight  
Dietary protein and calorie intake (4 day diary)  
Calculated normalised protein catabolic rate (nPCR)  
Serum albumin  
Anthropometric parameters (MAMC)  
Plasma potassium



## Demographics

| Variable      | Control<br>N=67 | Study<br>N=67 |
|---------------|-----------------|---------------|
| Age           | 54.77±2.34      | 54.78 ± 2.56  |
| DM            | 36%             | 37%           |
| Others        | 64%             | 63%           |
| Male          | 51%             | 52%           |
| Female        | 49%             | 48%           |
| Caucasians    | 52%             | 52%           |
| Blacks/Asians | 48%             | 48%           |

### Baseline characteristics

| Variable              | Control      | Study         | P value |
|-----------------------|--------------|---------------|---------|
| Weight Kg             | 74.94±11.45  | 76.62±21.14   | ns      |
| Systolic BP mmHg      | 123.65 ±1.17 | 124.04 ±1.34  | ns      |
| Diastolic BP mmHg     | 75.38 ±1.9   | 76.07 ±1.48   | ns      |
| MAMC cm               | 24.77±2.43   | 24.59±2.93    | ns      |
| Albumin G/L           | 35.10 ±0.78  | 34.65 ±0.54   | ns      |
| Bicarbonate mmol/L    | 19.93±1.47   | 19.79±2.16    | ns      |
| Phosphate mmol/L      | 1.48 ±0.04   | 1.42 ±0.038   | ns      |
| Urinary Na mmol/24h   | 140.09 ±7.91 | 140.04 ± 4.37 | ns      |
| Urinary Protein g/24h | 1.79 ±0.20   | 1.74 ±0.78    | ns      |

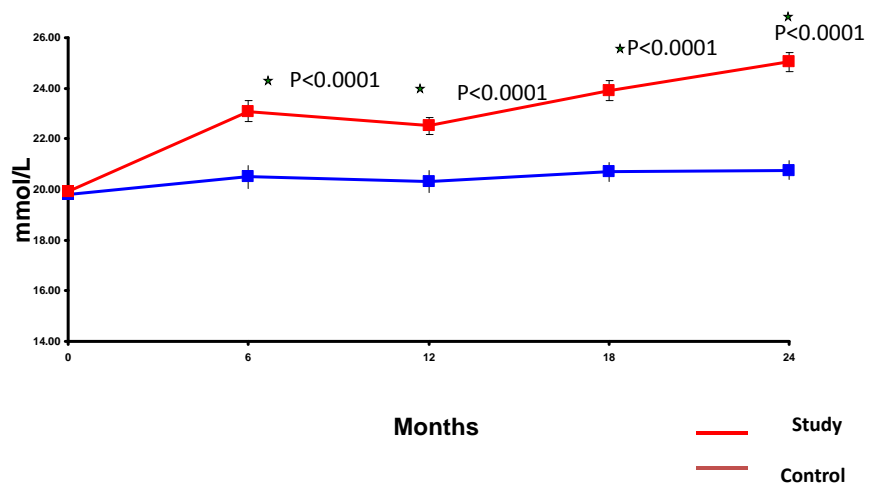
## RESULTS

### Effects on Progression of Renal Failure

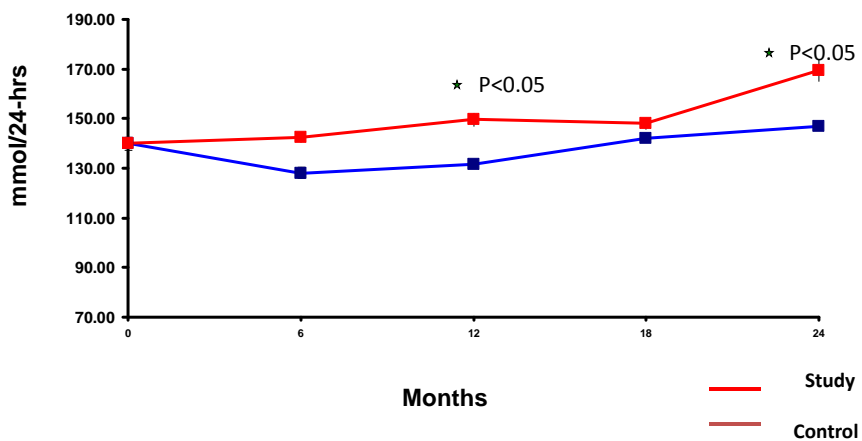
### Effects on Nutritional Status

### Average bicarbonate levels during the course of study

Mean bicarbonate dose = 1.8 g/d

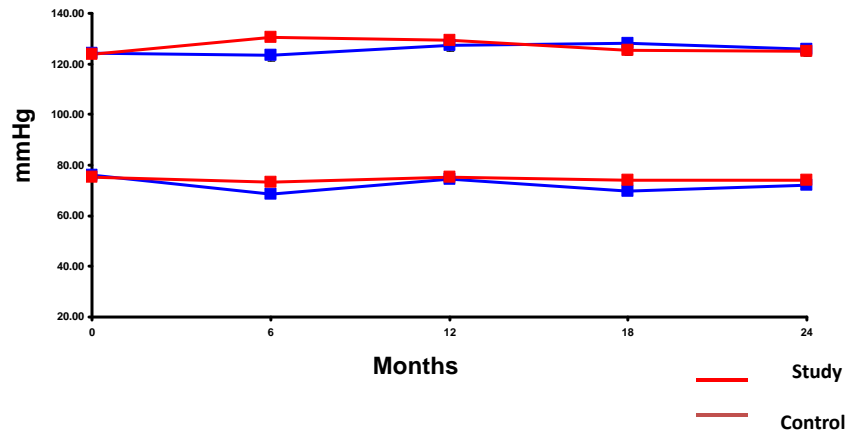


### Average urinary sodium levels during the course of study

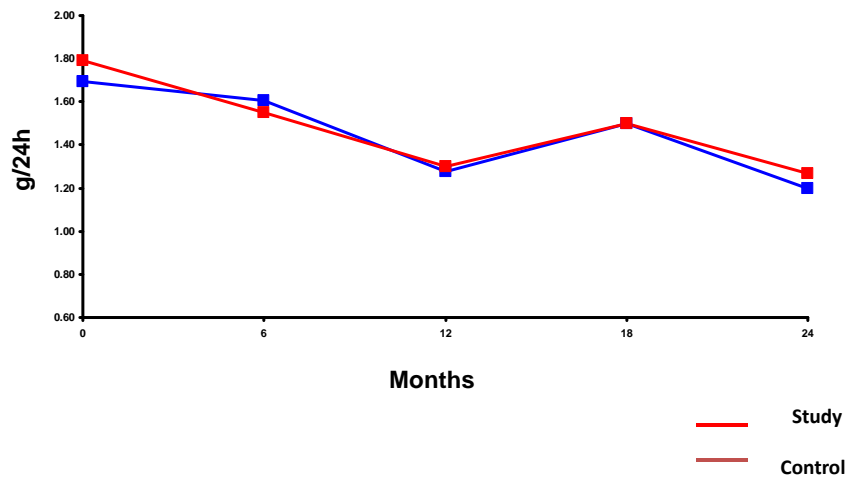


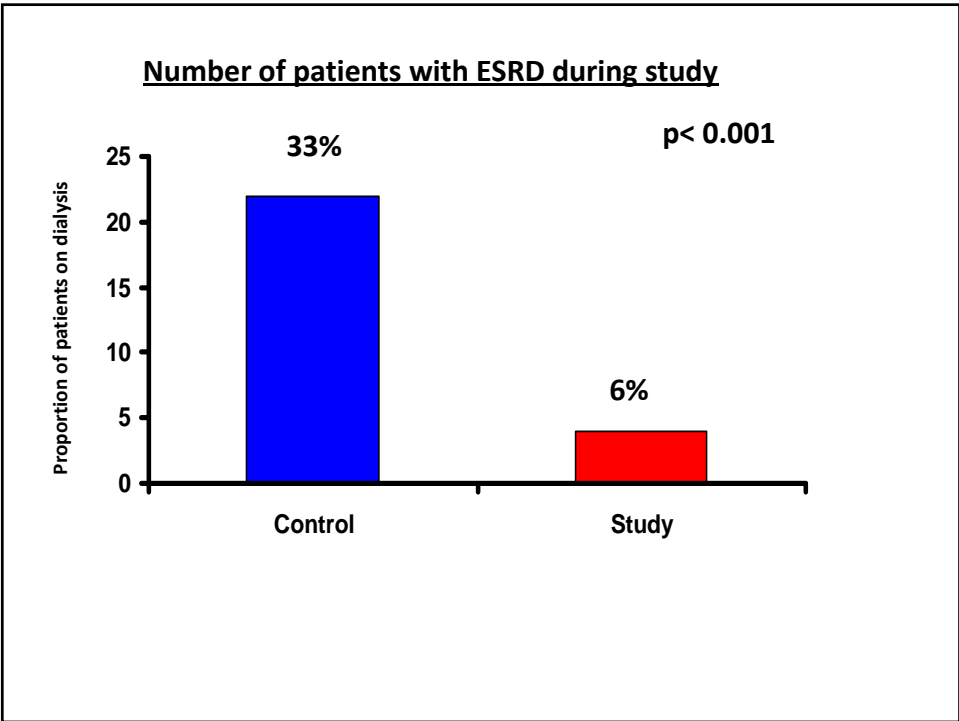
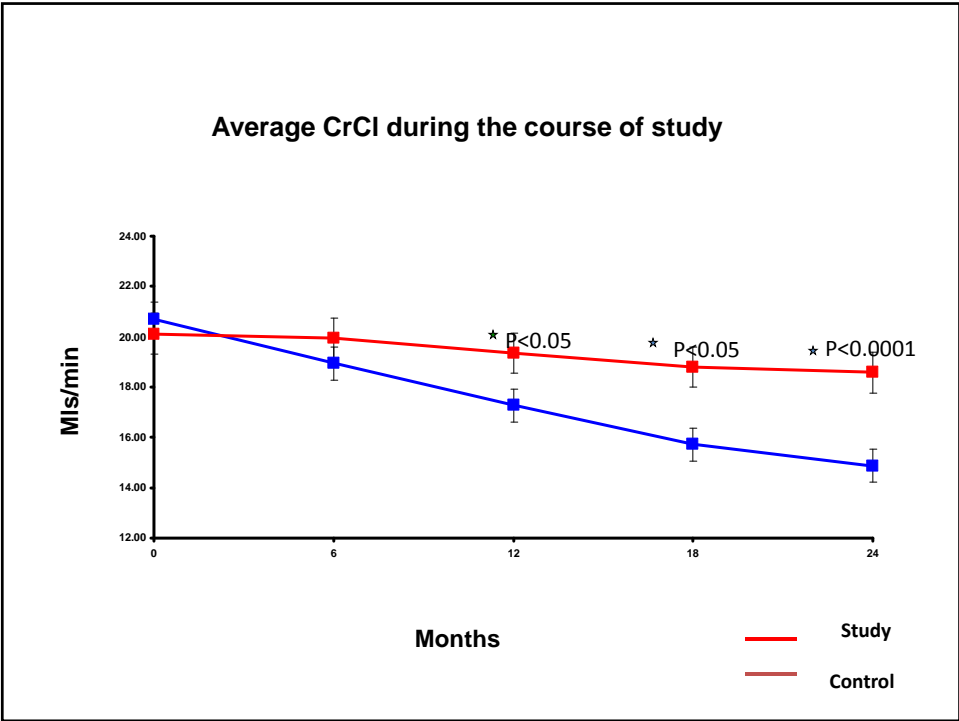


Average blood pressure during the course of study



Average proteinuria levels during the course of study





**Multivariate analysis for progression of CKD and ESRD**

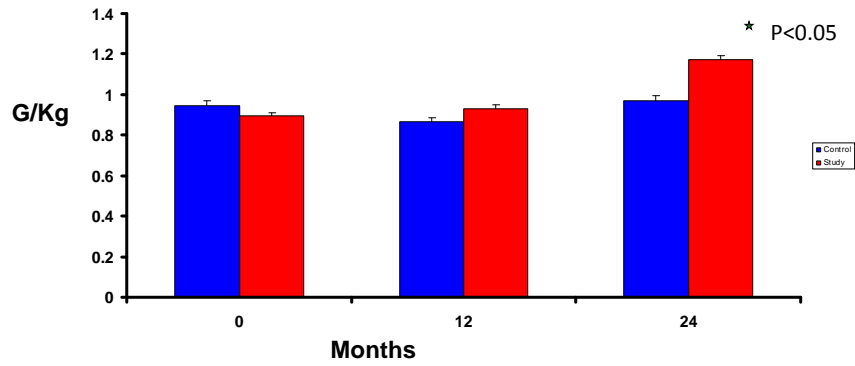
|                   |         |
|-------------------|---------|
| Age               | 0.024   |
| Gender            | 0.044   |
| Bicarbonate group | <0.0001 |

**RESULTS**

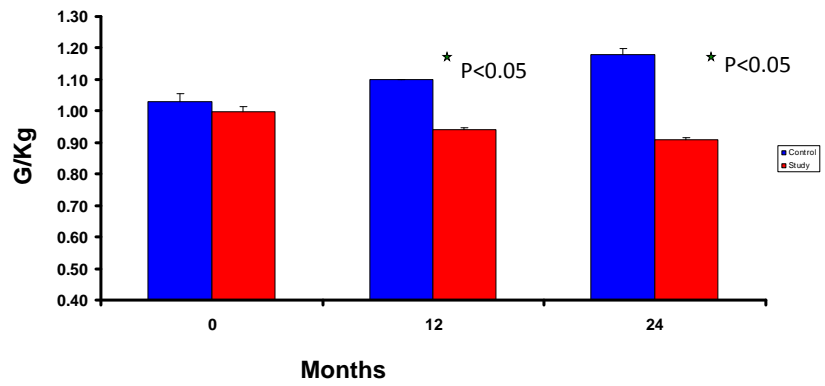
Effects on Progression of Renal Failure

**Effects on Nutritional Status**

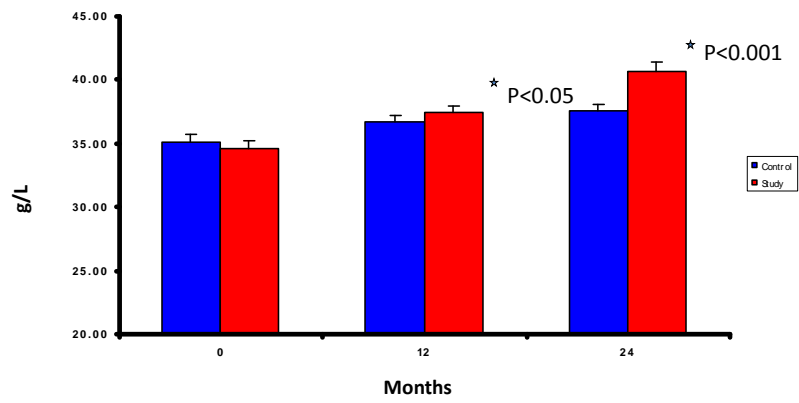
Average dietary protein intake during the course of study



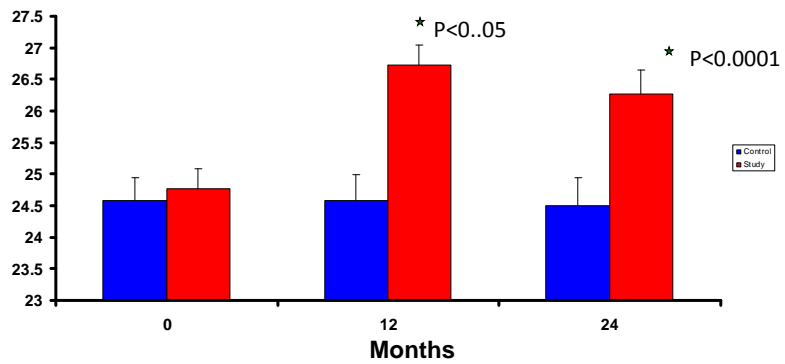
Average nPCR values during the course of study



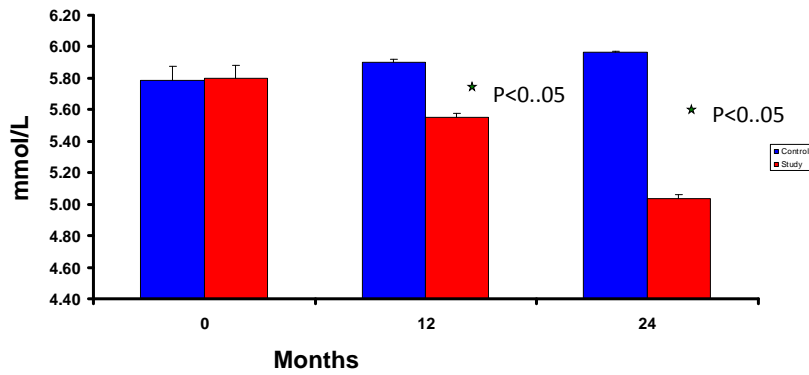
Average albumin levels in the control and study groups during the course of study



Average MAMC during the course of study



**Average serum potassium levels during the course of study**



**Multivariate analysis (dependent variable MAMC)**

**BMI** <0.0001

**Gender** <0.0001

**Bicarbonate group** <0.0001

## **Correction of Acidosis in Patients with CKD stage 4 and 5 by Sodium Bicarbonate**

- 1. Slows the Rate of Progression of Renal Failure**
- 2. Delays the development of ESRD**
- 3. Improves Nutritional Status**
- 4. Safe, cheap and well tolerated.**

## **CONCLUSIONS**

**We recommend that mild to moderate acidosis in patients with CKD stage 4 and 5 with good blood pressure control and without overt CHF, treatment with oral sodium bicarbonate should be considered.**

## Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status

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Department of Renal Medicine and Transplantation, William Harvey Research Institute and Barts and the London NHS Trust, London, United Kingdom

## Metabolic Acidosis and Progression of Chronic Kidney Disease

Lynda A. Frassetto and Chi-yuan Hsu  
Department of Medicine, University of California San Francisco, San Francisco, California

*J Am Soc Nephrol* 20: 1869–1870, 2009  
doi: 10.1681/ASN.2009070710

CHRONIC KIDNEY DISEASE

## Oral bicarbonate: renoprotective in CKD?

Csaba P. Kovcsdy and Kamvar Kalantar-Zadeh

## Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR

*Kidney International* advance online publication, 13 January 2010;

**Table 1 | General demographic characteristics, SBP, Pcr, and eGFR at study entry in subjects before they were not treated (No-NaCit) or treated (NaCit) with Na<sup>+</sup> citrate**

|                          | No-NaCit (n=29) | NaCit (n=30) | P-value |
|--------------------------|-----------------|--------------|---------|
| Males (%)                | 48              | 47           | 0.891   |
| Black/white/Hispanic (%) | 55/14/31        | 53/23/23     | 0.591   |
|                          | Mean ± s.d.     | Mean ± s.d.  |         |
| Age (years)              | 53.9 ± 5.0      | 54.1 ± 6.4   | 0.928   |
| SBP (mm Hg)              | 160.5 ± 8.9     | 161.8 ± 10.8 | 0.611   |
| VTCO <sub>2</sub> (mm)   | 20.6 ± 0.8      | 20.8 ± 1.2   | 0.375   |
| Pcr (mg/dl)              | 3.20 ± 0.89     | 3.27 ± 0.70  | 0.733   |
| eGFRcr (ml/min)          | 33.4 ± 8.4      | 33.0 ± 8.5   | 0.871   |
| Pcys (mg/l)              | 3.86 ± 1.09     | 3.88 ± 0.79  | 0.936   |
| eGFRcys (ml/min)         | 32.3 ± 8.1      | 31.7 ± 8.3   | 0.767   |

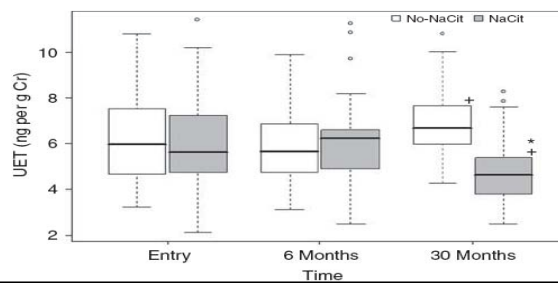
Abbreviations: eGFR, estimated glomerular filtration rate; N, number of subjects per group; Pcr, plasma creatinine; Pcys, plasma cystatin C; SBP, systolic blood pressure; VTCO<sub>2</sub>, venous serum total CO<sub>2</sub>.



**Table 2 | SBP, Pcr, and eGFR before (0 months) and after 24 months of No-NaCit vs NaCit**

|                    | No-NaCit (n=29) |             |                         | NaCit (n=30) |             |                         | P-value, NaCit vs No-NaCit |              |
|--------------------|-----------------|-------------|-------------------------|--------------|-------------|-------------------------|----------------------------|--------------|
|                    | Month 6         | Month 30    | P-value, 30 vs 6 months | Month 6      | Month 30    | P-value, 30 vs 6 months | Month 6                    | Month 30     |
| SBP                | 132.1 ± 6.3     | 131.9 ± 3.8 | 0.870                   | 132.4 ± 6.2  | 132.7 ± 5.7 | 0.761                   | 0.839                      | 0.490        |
| Pcr (mg/dl)        | 3.30 ± 0.91     | 4.24 ± 1.55 | <0.0001                 | 3.31 ± 0.69  | 3.61 ± 0.78 | <0.0001                 | 0.954                      | 0.057        |
| eGFRcr (ml/min)    | 32.5 ± 8.3      | 24.9 ± 9.7  | <0.0001                 | 32.7 ± 8.2   | 29.5 ± 8.8  | <0.0001                 | 0.945                      | 0.066        |
| → Pcys (mg/l)      | 3.94 ± 1.10     | 5.24 ± 1.41 | <0.0001                 | 3.93 ± 0.80  | 4.33 ± 0.89 | <0.0001                 | <u>0.952</u>               | <u>0.005</u> |
| → eGFRcys (ml/min) | 31.7 ± 7.9      | 23.0 ± 6.05 | <0.0001                 | 31.4 ± 8.2   | 27.8 ± 7.4  | <0.0001                 | <u>0.885</u>               | <u>0.008</u> |

Abbreviations: eGFR, estimated glomerular filtration rate; Pcr, plasma creatinine; Pcys, plasma cystatin; SBP, systolic blood pressure.



## Future Directions

### External Validity

### Double Blind Placebo Control Study :

**Placebo vs Sodium Citrate vs Sodium Bicarbonate  
in native CKD and CAN patients**

