Acidosis in Chronic Kidney disease

M.M. Yaqoob
Barts and the London NHS Trust
& School of Medicine and Dentistry,
William Harvey Research Institute,
London, UK
Impact of RCTs and Cohort Studies on Clinical Care

Guidelines: A set of principles directing action.

Standards: A set of principles to which others should conform or be judged.

- RCTs
- OR / Cohort studies
- Case series/case reports
- Expert opinion
Conduct of RCTs in Nephrology Lags Medicine Subspecialties

Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients

WN Suki1, Y Toubia, J Lian, J Reed, D Elterman, L Garrett, BN Ling, S Chasan-Taber, MA Dixon, and SR Burke

Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.I., Manfred Olschewski, M.Sc., Johannes F.E. Ma, and Eberhard Lenz, M.D., for the German Diabetes

Vascular Disease in Advanced Chronic Kidney Disease and End-stage Renal Disease: A Randomized Controlled Trial


Results of a randomized controlled trial on statin use in dialysis patients had no influence on statin prescription.


Statin use in diabetic patients receiving and not receiving hemodialysis.
### Stages of Chronic Kidney Disease: A Clinical Action Plan

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
<td>Diagnosis and treatment,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment of comorbid conditions,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slowing progression,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVD risk reduction</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
<td>Estimating progression</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
<td>Evaluating and treating complications</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
<td>Preparation for kidney replacement therapy</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>Replacement (if uremia present)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

*Abbreviations: CVD, cardiovascular disease*
Prevalence and Awareness of CKD

- 15% of USA population (25 million)
- 5 million with eGFR < 30 ml/min
- Projected 600,000 on dialysis by 2010
- Family members of dialysis patients 47% CKD
- 16% Australia with CKD
- 0.78-1.1% poor Indian states with CKD

Awareness

- 24%
- 7%
- 11%
Prevalence of ESRD and Economics
Life expectancy at birth in relation to GDP per capita (Daniels et al.)
Projected changes in life expectancy in selected African countries with high HIV prevalence, 1995–2000

Average life expectancy at birth, in years


Botswana
Zimbabwe
Zambia
Uganda
Malawi


World Health Organization
UNAIDS
Economic growth

Malaysia/Turkey/S.Korea

UK/USA

Every Decade Life Expectancy Jumped 8 yrs

Life expectancy has increased more in the past 40 years than it has in the past 4000
Wolfenson, former Head, World Bank
Global Life Expectancy
-10,000 BCE - 2003

Source: Indur M. Goklany. “The Improving State of our World.” Washington, DC: Cato Institute, 2007. 36. Life expectancy is believed to have been 20-30 years prior to 1820. Age 25 is selected as an average.

Life expectancy has increased more in the past 40 years than it has in the past 4000 years.

Wolfenson, former Head, World Bank
Increasing Life Expectancy and Causes of Death

Omran AR 1971
Cornerstone of Proteinuric CKD Management

• Blood Pressure Control: < 130/80 or 125/75

• ARBs/ACEi (Escape)

• Optimal Glycaemic Control: HbA1c < 7.5%
Figure 4: Kidney survival
Acidosis and Protein Energy Wasting

- 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
Acidosis and Progression of CKD

• 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 (HCO₃ < 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 CKD:
- 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
Refusal of consent = 20
Not eligible = 30

5 patients withdrew

No Bicarbonate

67

Bicarbonate
(Oral NaHCO3 1–3 gm/d)

62
## Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control N=67</th>
<th>Study N=67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.77±2.34</td>
<td>54.78 ± 2.56</td>
</tr>
<tr>
<td>DM</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Others</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td>Male</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>Female</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>Caucasians</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>Blacks/Asians</td>
<td>48%</td>
<td>48%</td>
</tr>
</tbody>
</table>
## Baseline characteristics

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

- Study
- Control
Average proteinuria levels during the course of study
Average CrCl during the course of study

Months

Study

Control
Proportion of patients on dialysis

Number of patients with ESRD during study

Control: 33% p< 0.001
Study: 6%
## Multivariate analysis for progression of CKD and ESRD

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.024</td>
</tr>
<tr>
<td>Gender</td>
<td>0.044</td>
</tr>
<tr>
<td>Bicarbonate group</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
RESULTS

Effects on Progression of Renal Failure

Effects on Nutritional Status
Average dietary protein intake during the course of study

- **Control**
- **Study**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/Kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.85</td>
<td>0.85</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>0.85</td>
<td>0.85</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*P<0.05*
Average nPCR values during the course of study

Months

Control
Study

G/Kg

0 12 24

P<0.05

P<0.05
Average albumin levels in the control and study groups during the course of study

<table>
<thead>
<tr>
<th>Months</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35.00</td>
<td>35.00</td>
</tr>
<tr>
<td>12</td>
<td>35.00</td>
<td>40.00</td>
</tr>
<tr>
<td>24</td>
<td>35.00</td>
<td>45.00</td>
</tr>
</tbody>
</table>

### Statistical Significance
- *P* < 0.05
- *P* < 0.001
Average MAMC during the course of study

P < 0.0001

Control
Study

P < 0.05

P < 0.001
Average serum potassium levels during the course of study

- **0 months:**
  - Control: 5.40 mmol/L
  - Study: 5.60 mmol/L

- **12 months:**
  - Control: 4.40 mmol/L
  - Study: 5.80 mmol/L
  - *P<0.05*

- **24 months:**
  - Control: 4.60 mmol/L
  - Study: 5.20 mmol/L
  - *P<0.05*
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

Ione de Brito-Ashurst, Mira Varagunam, Martin J. Raftery, and Muhammad M. Yaqoob

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

doi: 10.1681/ASN.2009070710

CHRONIC KIDNEY DISEASE

Oral bicarbonate: renoprotective in CKD?

Csaba P. Kovesdy and Kamvar Kalantar-Zadeh
Future Directions

External Validity

Double Blind Placebo Control Study:

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