Why phosphate matters and how to choose therapy?

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Accelerated **aging** in ESRD CKD patients: CVD mortality

Why?

Foley AJKD
Remarkable improvement in ESRD survival in the 2000s

1-year mortality

What are the differences between the 90s and 2000s?
What clinical practices in the nineties might have increased dialysis mortality in a >5 year horizon?

USRDS

90s: Calcium-based binders (+calcitriol)

2000s: calcium-free binders: sevelamer and lanthanum
90s: Calcium-based binders

Calcium-based binders allowed phasing out aluminium-based binders.

**Pivotal NEJM trial, 1986:**

- Mean dose calcium carbonate 8.5 g (range 2.5–17) per day
- Mean *supplemental elemental calcium* 3.4 g/day (up to a maximum of 6.8 g/day)

Slatopolski, et al. NEJM 1986
The serum calcium concentration required to inhibit PTH secretion is 10-11 mg/dl.

Three approaches to minimize hyperparathyroidism:

1. **Calcium supplementation**
   - Ca-based P binders
     - Starting dose for calcium carbonate 1.5g elemental calcium. Up to twice these amounts or sometimes more may be necessary

2. **Dialysate calcium 3.0-3.5 mEq/l**

3. Control of serum phosphate

3. Vitamin D
Could the choice of phosphate binder have contributed to the difference in mortality between the 90s and the 00s?

1. What we know from the general population?

2. CKD data
Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access dataset and meta-analysis

Mark I Bolland, senior research fellow, Andrew Grey, associate professor, Alison Avenell, clinical research fellow, Greg D Gamble, research fellow, Ian R Reid, professor of medicine and endocrinology

**Myocardial infarction**

Hazard ratio 1.26, (95% CI 1.07 to 1.47), P=0.005

**Stroke**

Hazard ratio 1.19, (95% CI 1.02 to 1.39), P=0.03
The calcium tolerable upper intake level is lower for those > 50y.o. in the general population.

### Table 6-2 Calcium Tolerable Upper Intake Levels (UL) by Life Stage

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>UL</th>
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<tbody>
<tr>
<td>19–30 y</td>
<td>2500 mg</td>
</tr>
<tr>
<td>31–50 y</td>
<td>2500 mg</td>
</tr>
<tr>
<td>51–70 y</td>
<td>2000 mg</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>2000 mg</td>
</tr>
</tbody>
</table>

**Women (y)**
- Aged 19–50: 1000 mg
- Aged 51–70: 1200 mg
- Aged >70: 1200 mg

**Females**
- 19–30 y: 2500 mg
- 31–50 y: 2500 mg
- 51–70 y: 2000 mg
- > 70 y: 2000 mg

Mean age advanced CKD and ESRD patients in Spain 65 years!
Could the **choice of phosphate binder** have contributed to the difference in mortality between the 90s and the 00s?

1. What we know from the general population?

2. CKD data
Kidney failure also impairs the capacity to excrete excess calcium.

Everybody knows that calcium from calcium-based binders is not absorbed because it is provided with meals and is excreted in feces bound to phosphate.

Is it really so?
Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease

Kathleen M. Hill¹, Berdine R. Martin², Meryl E. Wastney², George P. McCabe³, Sharon M. Moe⁴, Connie M. Weaver² and Munro Peacock¹

Mean eGFR 36 ml/min/1.73m² (range 26-53)
Normal baseline serum phosphate
Calcium carbonate

Hill et al. KI 2013
In CKD 1500 mg/d elemental calcium (as carbonate) decreases urine P but does not decrease phosphate balance. Where is excess phosphate going?
In CKD 1500 mg/d Calcium carbonate results in positive (non-bone) calcium balance

Calciuria does not increase (eFG 36 ml/min)

Hill et al. KI 2013
Where did excess P and excess Ca go?
Can u spot
the positive phosphate balance
and
the positive (non-bone) calcium balance?

U have to actually look for it!!
Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis

Sophie A Jamal, Ben Vandermeer, Paolo Raggi, David C Mendelssohn, Trish Chatterley, Marlene Dorgan, Charmaine E Lok, David Fitchett, Ross T Tsuyuki

- **Systematic review** up until Oct 22, 2012,

- **All randomised** and **non-randomised trials** that compared outcomes between patients with CKD taking
  - **calcium-based** phosphate binders (calcium carbonate or acetate) with those taking
  - **non-calcium-based** binders: sevelamer or lanthanum

- **Meta-analysis** of combined data from **randomised trials** to assess the primary outcome of **all-cause mortality**
Meta-analysis of 11 RCTs disclosed a survival advantage for calcium-free P binders

Risk of death reduction 22%
Non-calcium binders were associated with decreased coronary artery calcification.

Figure 5: Coronary artery calcification, according to length of follow-up

Jamal et al. Lancet 2013
Calcium-based P binders for the elderly: The straw that broke the camel’s back!!

La gota que colma el vaso

The drop that spills the glass
Calcium-based P binders for the **young**: so far, so good!!
CORONARY-ARTERY CALCIFICATION IN YOUNG ADULTS WITH END-STAGE RENAL DISEASE WHO ARE UNDERGOING DIALYSIS

WILLIAM G. GOODMAN, M.D., JONATHAN GOLDIN, M.D., PH.D., BEATRIZ D. KUIZON, M.D., CHUN YOON, M.D., PH.D., BARBARA GALES, R.N., DONNA SIDER, R.N., YAN WANG, PH.D., JOANIE CHUNG, M.S., ALETHA EMERICK, LLOYD GREASER, M.P.H., ROBERT M. ELASHOFF, PH.D., AND ISIDRO B. SALUSKY, M.D.

2000

So far so good!
CORONARY-ARTERY CALCIFICATION IN YOUNG ADULTS WITH END-STAGE RENAL DISEASE WHO ARE UNDERGOING DIALYSIS

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All patients were <30 y.o.

So far so good!

Accelerated aging in ESRD CKD patients: CVD mortality
Those who cannot remember the past are condemned to repeat it

Jorge Agustín Nicolás Ruiz de Santayana y Borrás, known as George Santayana
(December 16, 1863 – September 26, 1952
A lifelong Spanish citizen

I have learned from my mistakes, and I am sure that I can repeat them exactly
This time is different!

implications of additional therapeutic approaches
61-year-old male, stage 5 CKD, DM

- **Ideos** (Calcium carbonate, 1000 mg elemental calcium /Cholecalciferol 800 UI)
- Calcitriol 0.25 micrograms four times a week
- Calcium carbonate, 3000 mg elemental calcium

**Cinacalcet 30 mg/d**
Calcific uremic arteriolopathy while on cinacalcet.

Gonzalez-Parra E, Martin-Cleary C, Martin J, Ortiz A.

Department of Nephrology, IIS-Fundacion Jimenez Diaz and Autonomous University

Caution is required during simultaneous use of NaHCO3 and calcium carbonate.

Calcium carbonate can cause milk alkali syndrome and vessel calcification. Therefore, calcium carbonate should not be used as the primary alkalinization agent for CKD patients.

What about the use of calcium-based phosphate binders that contain alkali?
Acid-base and vascular calcification


Will the Lancet paper impact clinical practice?

Hierarchy of evidence

<table>
<thead>
<tr>
<th>Type of study</th>
<th>RCT</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Simvastatin/ezetimibe vs placebo</td>
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<tr>
<td>Number of patients</td>
<td>9270</td>
</tr>
<tr>
<td>Follow-up</td>
<td>59 mo</td>
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<tr>
<td>CKD stage</td>
<td>Non-dialysis+dialysis</td>
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<tr>
<td>Outcome</td>
<td>CV events 17%</td>
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<tr>
<td>Reference</td>
<td>Baigent (SHARP), Lancet 2011</td>
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<tr>
<td>Cholesterol</td>
<td>Simvastatin/ezetimibe vs placebo</td>
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<tr>
<td>Phosphate</td>
<td>Ca vs non-Ca P binder</td>
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</tbody>
</table>
Is Jamal’s study a game changer in the choice of phosphate binders?

High-quality metaanalyses and systematic reviews of randomised controlled trials can be used as evidence to support a recommendation.