Role of Transport and Kinetics in Growth of Renal Stones

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The risk of astronauts developing kidney stones has become a serious issue.

A recent survey of renal stone formation in US astronauts has revealed a total of 14 episodes (Pietrrzyk et al, 2007).

Some of these episodes occurred in the preflight period (n=5) while others (n=9) were in the post flight phase.

Multiple stone events also reported among the Soviet cosmonauts with one reported episode of in-flight renal stone occurrence that nearly resulted in mission abortion (Sibonga et al, 2008).
Renal Biochemistry Alteration in Microgravity

- The physiological, environmental and dietary conditions of space travel increase the risk for development of renal stones.
  - Bone atrophy $\Rightarrow$ increased concentration of calcium
  - Dehydration & the lower urine output $\Rightarrow$ reduced urine volumes
  - high sodium and animal protein diet $\Rightarrow$ increased salt - low pH
  - low urinary citrate and magnesium $\Rightarrow$ lack of sufficient stone-forming inhibitors
- These factors all provide favorable conditions for promoting increased crystallization and agglomeration (Whitson, 2010).
Renal Stone Growth Model
Kassemi et al (JCG, 2011)

- Balance between *transport* and *surface reaction* determines concentration of Ca and Ox at the surface of stone.
- Surface concentrations determine the growth rate.
Combined Reaction-Transport Model for Renal Stone Growth

2nd Order Surface Reaction:

\[ \frac{dr}{dt} = K_G \cdot V_m \cdot K_s^{1/2} \left\{ \left[ \frac{C_{ca}^* \cdot C_{ox}^* \cdot f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2 \]

Balance Between Transport & Reaction:

\[
\begin{align*}
K_m (C_{ca}^* - C_{\infty ca}^*) &= -K_G K_s^{1/2} \left\{ \left[ \frac{C_{ca}^* \cdot C_{ox}^* \cdot f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2 \\
K_m (C_{ox}^* - C_{\infty ox}^*) &= -K_G K_s^{1/2} \left\{ \left[ \frac{C_{ca}^* \cdot C_{ox}^* \cdot f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2
\end{align*}
\]

Damkohler Number

\[ Da = \frac{K_G}{K_m(d)} \]

Relative Supersaturation

\[ RS = \left[ \frac{C_{ca}^* \cdot C_{ox}^* \cdot f_2^2}{K_s} \right]^{1/2} \]
# Impact of Microgravity On Renal Biochemistry

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Primary Effect</th>
<th>Secondary Effect</th>
<th>Super Saturation (RS)</th>
<th>Reaction Rate, $K_G$ (or Da)</th>
<th>Nucleation Rate ($N_0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Ca ↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxalate</td>
<td>Ox ↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td>Uric Acid Nidus</td>
<td>Ca ↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal Ca Reabs</td>
<td>Ca ↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Renal Ca Reabs</td>
<td>Ca</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Vitamin D</td>
<td>Ca</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Intestinal Ca Abs</td>
<td></td>
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<tr>
<td>Salt Nidus</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Protein</td>
<td>pH ↓</td>
<td></td>
<td></td>
<td></td>
<td>$N_0$ ↑</td>
</tr>
<tr>
<td></td>
<td>Renal Ca Reab</td>
<td>Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inorganic Inhibitor (K-Mg-Ci)</td>
<td>Ca ↑</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ox ↑</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$K_G$ ↑</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Organic Inhibitor (Glycosaminoglycans)</td>
<td>$K_G$</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Effect of Solution Supersaturation on CaOx Growth Rate

Meyer & Smith (1975):
\[ K_r = 22 \text{ (cm/sec) (liter/mole)} \]

Milan et al. (1998):
\[ K_G = 2.5 \times 10^{11} \text{ (m/sec)} \]

Conversion:
\[ K_G = K_r K_s^{1/2} V_m \]

\[ K_G = 5.0 \times 10^{11} \text{ (m/sec)} \]
Microgravity Parametric Shift

Transport

\[ \text{drift (cm/min)} \]

\[ 1G \]

\[ \mu G \]

\[ K_G \]

\[ RS_\infty \]

\[ S_\alpha = RS_\infty - 1 \]

\[ \text{Da} = 0.00015 \]

\[ \text{Da} = 0.0015 \]

\[ \text{Da} = 0.015 \]

\[ \text{Da} = 1 \]

\[ \text{Da} = 10 \]
Case Studies: Renal Stone Growth on Earth & in Space

Microgravity is marked by increased Ca concentration, lower inhibitor concentration and unaltered urine flow rate.

<table>
<thead>
<tr>
<th>Case</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earth - Normal</td>
<td>• Low super-saturation</td>
</tr>
<tr>
<td></td>
<td>• 75% reduction of reaction constant by inhibition</td>
</tr>
<tr>
<td>Earth - Stone Former</td>
<td>• High super-saturation</td>
</tr>
<tr>
<td></td>
<td>• No reduction of reaction constant by inhibition</td>
</tr>
<tr>
<td>Microgravity - Normal</td>
<td>• Moderately high super-saturation</td>
</tr>
<tr>
<td></td>
<td>• 50% reduction of reaction constant by inhibition</td>
</tr>
<tr>
<td>Microgravity - Stone Former</td>
<td>• Very high super-saturation</td>
</tr>
<tr>
<td></td>
<td>• No reduction of reaction constant by inhibition</td>
</tr>
</tbody>
</table>

• Uninhibited reaction constant from Meyer Smith (1975): $Kr = 22 \text{ (cm/sec) (liter/mole)}$
• $C_{\text{ica}} / C_{\text{iox}} = 10$
1G Comparison: Normal versus Stone-Former
Microgravity Versus 1G Comparisons for Normal and Stone-Former
Effect of Citrate on Growth Rate for Stone Former in Microgravity

Effect of Urine Citrate Concentration on CaOx Reaction rate co-related from published data (L. Wang et al, JCG, 2006)
The previous prediction were based on growth as the only mechanism for increasing the stone size.

The renal calculi problem is not a single stone event but a multiple stone phenomena.

Stones can also change size by agglomeration and breakage.

A new mathematical framework is needed for enhancing the model to include the effects of calculi interaction.
Future Directions: Nucleation, Agglomeration, Breakage

Kavanagh (2004): *Kidney is not a beaker but a Continuous Crystallizing Chemical Reactor*
Future Directions: Population Balance Framework
(Randolph & Larson 1988)

**Physical Flow CV (Nephron)**

\[ G = \frac{dV}{dT} \]

**Imaginary Growth CV**

Population Balance Equation

\[
\frac{\partial}{\partial t}[n(V,t)] + \nabla \cdot [\bar{w}(V,t)] + \nabla_V \cdot [G_v n(V,t)] = \frac{1}{2} \int_0^V a(V-V',V') n(V-V',t)n(V',t) dV' - \int_0^\infty a(V,V') n(V,t) n(V',t) dV' + \int_\Omega \nu g(V') \beta(V/V') n(V',t) dV' - g(V)n(V,t)
\]

Birth due to Aggregation
Death due to Aggregation
Birth due to Breakage
Death due to Breakage
Microgravity Versus 1G Comparisons
Stone Size Distribution for Normal Subject

1G Normal

1G Stone-Former

Microgravity Normal
Conclusions

● A combined kinetics-transport model for growth of renal calculi was developed and validated against published data.

● Our numerical results point to three interesting and important trends:
  - **Adverse effect of microgravity** seems to be relatively greater for a non-stone-former than for a stone-former – This may prove important to astronaut screening protocols.
  - Administration of inorganic inhibitors such as **citrates may provide an effective countermeasure for reducing the risk of renal stone** development in space - even for inherent stone-formers.
  - **Growth rates in microgravity will most likely be transport-limited** and not determined by the surface reaction rate - as assumed a priori in most other predictive models.

● The Growth model was cast into a PBE framework:
  - Account for the important effects of **agglomeration and breakage**.
  - Predict evolution in renal **calculi size distributions** (CSD)
Extra Backup Slides
Preliminary Validation of the Renal PBE  
(Finlayson, 1972)

**Finlayson’s Single Stage Continuous Crystallizer**

- In-Flow: CaCl$_2$, K$_2$C$_2$O$_4$, NaCl
- $\tau = V/Q = 55$ min
- $G = .0008$ mm/min

\[
\frac{\partial n(t,r)}{\partial t} + G \cdot \frac{\partial n(t,r)}{\partial r} = \frac{-n}{\tau}
\]