Calcium - Why does it form, what is the pathophysiology and is there a medical treatment on the horizon?

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Disclosure

Dr. Raghu Kolluri reports following –

- **Uncompensated Consultant/Advisor**—Boston Scientific, Intact Vascular, InterVene, Medtronic, Pedra, Philips, Thrombolex, Vesper Medical
- **Executive Board Member** – VIVA Physician Inc, a 501c3 Corp
Not all plaque is created equal

<table>
<thead>
<tr>
<th>Types of Vascular Calcification</th>
<th>Location and Features</th>
<th>Associated Condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcific atherosclerosis</td>
<td>Intimal; ossification</td>
<td>Atherosclerosis, hyperlipidemia; osteoporosis; hypertension; inflammation</td>
</tr>
<tr>
<td>Calcific medial vasculopathy</td>
<td>Tunica media</td>
<td>Type 2 diabetes mellitus; end-stage renal disease; hyperphosphatemia; amputation</td>
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<td>(Mönckeberg’s medial calcific sclerosis)</td>
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<tr>
<td>Elastocalcinosis</td>
<td>Internal elastic lamina</td>
<td>Pseudoanxthoma elasticum; Marfan syndrome</td>
</tr>
<tr>
<td>Calcific uremic arteriolopathy</td>
<td>Microvessels; amorphous</td>
<td>End-stage renal disease; warfarin (?</td>
</tr>
</tbody>
</table>


Vascular Calcification

- Reactive –
  - To mechanical strain, inflammation, reactive oxygen species, and local metabolites
  - Maladaptive response to stress

- Proactive –
  - Vascular smooth muscle cells may acquire an osteogenic and calcigenic phenotype to perpetuate arterial ossification

Catheter Cardiovasc Interv. 2014 May 1; 83(6): E212–E220
Medial Calcification - Monckeberg medial calcinosis

Stage 1

Stage 2
- Vascular calcifications composition = bone minerals
- **Vascular calcification of the media (VCm) = deposits of hydroxyapatite with a high degree of crystallization**

Stage 3

Stage 4

European Heart Journal (2014) 35, 1515–1525
Although medial calcification does not generally result in luminal obstruction, the decrease in the arterial vessel wall compliance $\rightarrow$ atherosclerosis, reduced perfusion, and eventually, CAD and PAD

European Heart Journal (2014) 35, 1515–1525
ATM - Ataxia-telangiectasia mutated
PARPs - poly[ADP-ribose] polymerases
SASP - Senescence-associated secretory phenotype
PAR - poly[ADP-ribose]
ECM - extracellular matrix

Plaque progression and regression

**Plaque progression**
- M1 → M2
- Persistence of chronic inflammation:
  - Sustained expression of pro-inflammatory cytokines: TNF-α, IL-6, etc
  - Apoptosis/Matrix vesicles
  - Impaired osteogenesis and osteoblastic maturation

**Plaque regression**
- OSM? Oncostatin M
- Statins?
- Resolution of chronic inflammation:
  - Expression of anti-inflammatory cytokines: IL-10
  - Ordered osteogenesis and stabilizing plaques

**Diagram**
- Necrotic core
- Microcalcification
- Macrophages
- Macrophages
- Microlcification
- Collagen
- Necrotic core
- Macrolcification
Management

- Intimal – Atherosclerosis
  - Prevent MACE/MALE - Rx hypercholesterolemia, hypertension, diabetes, smoking, obesity, and physical inactivity

- Medial – DM, Metabolic Syndrome, CKD (Associated with secondary Hyperparathyroidism)
  - All of the above
  - Calcium free phosphate binders
  - Vitamin D Analogs?

- Calciphylaxis
  - Sodium thiosulphate
  - Vitamin K
Statins

- Actions on plaque morphology
  - Regression of atheroma and increment of calcified deposits.
  - May facilitate the healing process against plaque inflammation by enhancing M2 polarization of macrophages, resulting in increased plaque calcification (macro calcification) as well as plaque regression.
Summary

- Expansion of our understanding of vascular calcification
- Various types of vascular calcification
- Multiple origins of calcifying vascular cells
- Increasing number of signaling pathways that influence vascular calcification

- Numerous possibilities for targeting vascular calcification in clinical contexts.
- The challenge -- translate knowledge into viable preventive and therapeutic strategies.