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Rickets
Phosphate & Iron Metabolism
PhD: Rickets in The Gambia
MRC CDF

25% of British children in the 18th and 19th centuries

Rickets “English Disease”

- Rickets: defective calcification of the growth plates of long bones in children, producing characteristic deformities

Paterson D., Arch Dis Child, 1926

Most common non-communicable disease of the developing world


Rickets: Causes & Classification

Calcipaenic:
- Vitamin D deficiency
- Dietary Ca deficiency
- PTH + 1,25(OH)2D, 250HD3

Phosphopaenic:
- Urinary PO43- loss (FGF23 mediated)
- pO43-, PTH → FGF23


1. Phosphate homeostasis
   - Urinary phosphate excretion
   - Plasma phosphate

2. FGF23 and CKD

3. FGF23 and arterial calcification

↑ FGF23 is a predictor of mortality

Phosphate Metabolism: FGF23
**Iron Metabolism**

- Essential nutrient:
  - carrier of O₂ - haemoglobin
  - enzyme co-factors (CYPs)
  - Important for brain development

**Iron Deficiency Anaemia: 4 billion**

*Figure 3.1b Anaemia as a public health problem by country: Pregnant women*

- One of the most common nutrient deficiencies (50% of population in developing world)

**MRC Keneba, The Gambia**

- A poor, rural farming African village
- UVB-skin exposure for vitamin D synthesis
- Low Ca intakes: 200-400 mg/d
- High rates of iron deficiency
- Growth faltering, stunting, delayed puberty
- Rickets

**Rickets in The Gambia**

- ↑25OHD
- ↑PTH and 1,25(OH)₂D
- ↓dietary calcium
- ↑ALP
- ↓plasma phosphate
- ↑urinary phosphate excretion
- ↑FGF23


**Rickets in The Gambia**

- Elevated FGF23 associated with poor iron status
  - Poor iron status inversely associated FGF23 concentration
  - FGF23 decreases after supplementation with ferrous sulphate

MRC Career Development Fellowship

- **FGF23 & Iron Pathways and bone health:**
  1. Maternal iron status and infant bone mineral metabolism in The Gambia
      • Dr S Moore MRC HNR, Cambridge and The Gambia
  2. FGF23 & Phosphate loss in HIV positive women in South Africa
      • Dr M Hamill MRC HNR, Cambridge
  3. Iron supplementation trial and bone mineral metabolism in the iron deficient Cambridge women
      • Dr D Pereira MRC HNR, Cambridge
  4. Rickets in Malawi

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Maternal Nutrition in Gambian mothers—
Effects on infant epigenetics

Maternal nutrition at conception modulates DNA methylation of human metastable epialleles

> Does maternal iron deficiency influence infant FGF23 regulation?

- ENID trial (ISRCTN492825450)
  - n=700 mother-infant pairs (PI. Dr Moore) MRC Keneba, The Gambia
- **Maternal:** blood sample, anthropology at booking, week 20 and week 30
- **Infant:** blood sample and anthropology in cord blood, and week 12, 24, 52, 78 and 104


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Iron deficient mice during pregnancy—
offspring with altered phosphate homeostasis and bone

Does maternal iron deficiency influence infant FGF23 regulation?

- Relate maternal iron status to infant bone mineral metabolism:
  - Plasma phosphate and FGF23
  - Anthropometry
  - Bone mineral density (DXA)

- Maternal nutrition on infant bone health and antecedents of rickets.
Conclusions

- Rickets is re-emerging in the UK and is the most common non-communicable disease in children of the developing world
- Rickets in The Gambia combination of calcium deficiency and phosphate disruption modulated by iron deficiency?
  - Investigating novel links between iron and phosphate pathways
  - Maternal iron deficiency during pregnancy involved in infant phosphate metabolism, bone health and rickets?
  - Implications for maternal nutrition