Does early nutrition program later bone health in preterm infants?

MS Fewtrell

Childhood Nutrition Research Centre, UCL Institute of Child Health, London
Osteoporosis

UK annual costs to NHS close to the figure for treating CVD

Lifetime risk of fracture in women similar to the risk of CVD

1/6 women sustain hip fractures – 1/9 breast cancer
Peak bone mass

Bone mass

Age

10 20 30 40 50 60 70
**Fetal mineral accretion mmol/kg/day**

90% of mineral accretion occurs during the last trimester
Metabolic bone disease of prematurity

Inadequate calcium and phosphorus intake

Undermineralised bones

Fractures

Often asymptomatic at the time
Does it have long-term consequences for bone health?
Randomised trial - recruitment 1982-85

926 infants, <1850g

Does mother want to provide breast milk?

No
Trial 1

DBM v PTF
Cambridge
Ipswich
Kings Lynn

TF v PTF
Norwich
Sheffield

Yes
Trial 2

DBM+MBM v PTF+MBM

TF+MBM v PTF+MBM
## Composition of trial diets

<table>
<thead>
<tr>
<th></th>
<th>PTF</th>
<th>TF</th>
<th>DBM</th>
<th>MBM</th>
<th>Modern preterm formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/dl)</td>
<td>2.0</td>
<td>1.5</td>
<td>1.3</td>
<td>1.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Energy (kcal/dl)</td>
<td>80</td>
<td>68</td>
<td>&lt;50</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>Fat (g/dl)</td>
<td>4.9</td>
<td>3.8</td>
<td>2.0</td>
<td>3.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>70</td>
<td>35</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>35</td>
<td>29</td>
<td>17</td>
<td>14</td>
<td>50</td>
</tr>
</tbody>
</table>
### Neonatal mineral intakes mg/kg/day

<table>
<thead>
<tr>
<th></th>
<th>DBM</th>
<th>PTF</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Phosphorus</td>
<td>23.1 (6.2)</td>
<td>32.0 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium</td>
<td>46.2 (7.7)</td>
<td>66.4 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak ALP</td>
<td>992 (570)</td>
<td>766 (401)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

**Current recommended intakes:**
- >120mg/kg/day for calcium
- >62mg/kg/day for phosphorus
Follow-up studies

5 years
• Higher bone mass in subjects with greater neonatal consumption of human milk

10 -12 years
• No effect of neonatal diet on bone mass
• Higher osteocalcin in subjects who received lower nutrient diets
Early diet and peak bone mass: 20 year follow-up of a randomised trial in preterm infants

MS Fewtrell, JE Williams, A Singhal, PR Murgatroyd, N Fuller, A Lucas

Childhood Nutrition Research Centre, UCL Institute of Child Health, London
Addenbrooke’s Clinical Research Centre, Cambridge

Fewtrell et al. Bone 2009;45:142
20 year follow-up - hypotheses

1. Early diet programs peak bone mass and bone turnover

2. Human milk has a specific enhancing effect on peak bone mass

3. Preterm subjects have lower peak bone mass compared to population reference data
Outcome measures

**DXA**
Bone mass at whole body, hip, lumbar spine

**Bone turnover**
Formation  Osteocalcin  P1NP  BSALP
Resorption  CTX
Hypothesis 1: Effect of randomised diet

No effect of randomised diet on

- Weight
- Height
- Bone mass at any skeletal site
- Bone turnover
Hypothesis 2: Effect of human milk

Randomised comparison of DBM v PTF (n=13 v 12)
No significant difference in bone mass or turnover

DBM group had higher values.....

<table>
<thead>
<tr>
<th>Measure</th>
<th>Difference</th>
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<tbody>
<tr>
<td>WB bone area</td>
<td>5.7%</td>
</tr>
<tr>
<td>WB BMC</td>
<td>6%</td>
</tr>
<tr>
<td>LS bone area</td>
<td>8.6%</td>
</tr>
<tr>
<td>LS BMC</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
Human milk
Non-randomised analyses
Dose response relationship between whole body BMC and BA and the amount of MBM received during the neonatal period

No association between %MBM and later height or weight
‘Low’ versus ‘High’ human milk

Higher WB BA and BMC in ‘high’ human milk group

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<table>
<thead>
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<tbody>
<tr>
<td>BA</td>
<td>3.5%  (p=0.01)</td>
</tr>
<tr>
<td>BMC</td>
<td>4.8%  (p=0.03)</td>
</tr>
</tbody>
</table>
Hypothesis 3: Peak bone mass in subjects born preterm compared to population reference data
Height, BMI and lumbar spine BMD in preterm infants at 20 years

<table>
<thead>
<tr>
<th>Birthweight Category</th>
<th>Height SDS at 20 yrs</th>
<th>BMI SDS at age 20 yrs</th>
<th>LSBMD SDS at age 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1250g</td>
<td>0.20</td>
<td>1.00</td>
<td>0.20</td>
</tr>
<tr>
<td>&lt;1250g</td>
<td>0.00</td>
<td>0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td></td>
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</table>
Fractures

32% reported at least one fracture

No effect of randomised diet on % with fracture

No difference in bone mass between those with and without fractures
Which factors predict skeletal size and bone mass in early adult life?

Greater whole body bone size and bone mineralisation predicted by

- Greater current weight and height
- Higher neonatal human milk intake
- Greater height SD score at age 7
- Lower relative height gain from 7-20 years
Summary

1. Early randomised diet had no effect on later bone mass or turnover - despite large differences in early nutritional intake

Lower height and LS BMD in this cohort may not be directly related to sub-optimal mineral intake

? other effects of prematurity
Summary

2. Human milk is associated with higher bone size and bone mass - despite its low nutrient and mineral content

? Non-nutrient factors in breast milk
Breastfeeding and childhood bone mass in term infants

Breast-fed
Formula-fed

BMD (g/cm²)

Femoral neck
Lumbar spine
Whole body

p=0.05
p=0.007
p=0.001

Jones et al, Osteoporosis Int 2000;11:146-52
Study strengths and weaknesses

Unique RCT with long-term follow-up

BUT must consider

Attrition – study power, bias
Generalisability to modern neonates
Differences between diet groups were much greater than would occur in a modern NICU

- No mineral supplements
- No breast milk fortifiers
- All infants received vitamin D 800IU per day
Current recommended mineral intakes for preterm infants are high and difficult to meet especially using parenteral nutrition.

Are these high mineral intakes necessary for bone health?

Attempts to meet mineral requirements using parenteral nutrition solutions results in exposure to aluminium.
Neonatal aluminium exposure and later bone health

• no known biological function
• accumulates in the body if high exposure
  GI tract bypassed
  poor renal function

• preterm infants are exposed via parenteral nutrition – especially calcium gluconate
Randomised trial of standard versus aluminium-depleted PN solution in preterm infants

<table>
<thead>
<tr>
<th>Standard</th>
<th>Aluminium-depleted (AD)</th>
</tr>
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<tbody>
<tr>
<td>Calcium gluconate</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>K acid phosphate</td>
<td>Na-K phosphate</td>
</tr>
</tbody>
</table>

Neonatal aluminium exposure (mcg/kg)

Randomised diet in aluminium trial
Bone mass at age 15

- Lumbar spine BMC 0.7SD higher in AD group

- Hip BMC significantly lower (7%) in subjects with aluminium exposure >median, independent of body size

Fewtrell et al. Pediatr; 2009;124:1372
Aluminium exposure may adversely programme bone health

Relevant to contemporary infants – still exposed to aluminium via PN – especially from attempts to achieve high mineral intakes

Impossible to significantly reduce exposure with currently available solutions
Conclusions

1. Remarkably little apparent effect of early nutrient or mineral intake on later bone health ……modern neonates have a much higher mineral intake

2. Human milk associated with higher whole body bone mass and larger bones – potentially beneficial long-term
Acknowledgements

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Assessment of bone strength and geometry

Bone strength and resistance to bending and compression depends on
- material properties (mineral content)
- distribution of the mineral
- geometry of the bone

These parameters can be measured on DXA hip scans
Factors relating to hip strength in early adult life

Greater hip strength parameters predicted by

- Greater current weight and height
- Higher femoral neck BMC
- Lower relative height gain from 7-20 years

No effect of neonatal nutrition or MBD on measures of hip geometry or strength – including Hip Axis Length

No differences in hip bone mass or geometry between those with and without previous fractures