An unusual cause of hypocalcemia in a toddler

הכנסה של 13 "שור" ב"חג החלב" ועד
מרץ 2017

"ש"ר שירה לונדון
המכון האנדווריאטריה, מרכז רפואי העמק, עפולה
Case Presentation-History

- 3 years old male
- Family: Healthy 1st degree consanguineous parents of Arab Muslim decent
- Spontaneous delivery at 31w GA
- Birth weight 1836g (AGA)
- Transient hyponatremia and hyperkalemia in neonatal period
  - Elevated renin and aldosterone levels.
  - Normalized at age of 1 m
  - Transient Pseudohypoaldosteronism.
- Healthy, normal growth and normal psychomotor development
Case Presentation

- Hospitalized due to febrile convulsion at age 2.3 years.

Physical examination:
- Weight 11.6 kg (12th centile), Height 87 cm (20th centile)
- Tonsillitis

Laboratory Investigation:
- CBC: leukocytosis (WBC 15070, 77% neut.)
- Normal kidney and liver function tests
- Normal electrolytes (Na-135, K -4.47)
- Glucose 100
- Ca 6.17 mg/dl

Hypocalcemia
Therapy

- Calcium Gluconate I.V. -500 mg X 4/day
- Penicillin I.V. (for tonsillitis)
Ca$^{++}$ ↓

1α Hydroxylase ↑

25(OH)D 1,25(OH)$_2$D

1,25(OH)$_2$D ↑

Ca absorption

Ca reabsorption

↑ Phosphate excretion

↑ Bone resorption

PTH ↑
Causes of Hypocalcemia

I - Neonatal

A Maternal disorders
- Diabetes mellitus
- Toxemia of pregnancy
- Vitamin D def.
- Use of anticonvulsants
- Hyperparathyroidism

A Neonatal disorders
- LBW, prematurity, IUGR
- Asphyxia, sepsis, critical illness
- Hyperbilirubinemia, phototherapy, exchange transfusion
- Acute/chronic renal failure
- Nutrients/medications: high phosphate intake, bicarbonate, phytates, anticonvulsants

II - Hypoparathyroidism

A congenital
- Transient neonatal
- Congenital hypoparathyroidism
  - Familial isolated (AR, AD, X linked)
  - DiGeorge
  - Syndromic
- Insensitivity to PTH
  - Pseudohypoparathyroidism (PHP)-IA, IB, IC, II
  - Hypomagnesemia

B Acquired
- Autoimmune polyglandular syndrome type 1
- Activating Abs to the calcium sensing receptor
- Post surgical, radiation destruction
- Infiltrative (Hemochromatosis, Wilson)

III - Vitamin D deficiency

IV - Others

A calcium deficiency - nutritional
B Hypomagnesemia
C Hyperphosphatemia
Hypocalcemia

Mg++
- Low
- Normal

PTH
- Elevated
- Low/inapp. normal

25-OH-vitamin D
- Vitamin D sufficiency
- Vitamin D deficiency

Secondary Hyperparathyroidism:
- Malabsorption
- Vitamin D deficiency
- PHP 1,2
- VDDR 1,2

Hypomagnesemia

Hypoparathyroidism

Causes:
- GI losses
- Nutritional
- Low sun exposure
### Evaluation of hypocalcemia

- **Insufficiency**: 50-75 nmol/l, **deficiency**: <50 nmol/l

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>6.17</td>
</tr>
<tr>
<td></td>
<td>8.8-10.8 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5.16</td>
</tr>
<tr>
<td></td>
<td>3.8-6.5 mg/dL</td>
</tr>
<tr>
<td>Alk. Phosphatase</td>
<td>865</td>
</tr>
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<td></td>
<td>104-345 U/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.22</td>
</tr>
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<td>Vit D (25-OH)</td>
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<td>75-250 nmol/L*</td>
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<td>PTH</td>
<td>273.5</td>
</tr>
<tr>
<td></td>
<td>14.0-72.0 pg/mL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>3.8-5.4 g/dL</td>
</tr>
<tr>
<td>U Ca/Creatinine**</td>
<td>0.389</td>
</tr>
<tr>
<td></td>
<td>0-0.6</td>
</tr>
<tr>
<td>1,25 OH-Vit. D</td>
<td>357.0</td>
</tr>
<tr>
<td></td>
<td>39-160 pmol/L</td>
</tr>
</tbody>
</table>

- **Vitamin D deficiency**
- **Secondary Hyperparathyroidism**
- **Elevated 1,25OH-Vit. D**

*Insufficiency :50-75 nmol/l, deficiency: <50 nmol/l

**on IV calcium therapy**
Therapy

- Calcium Gluconate I.V. -500 mg X 4/day
- Penicillin I.V. (for tonsillitis)
- Calcium Sandoz P.O. - 250mg X 2/day
- Vitamin D (25OH)- 2000 U/day
Imaging

Rickets
Hypocalcemia

Mg++
- Low
- Normal

PTH
- Elevated
- Low/ inapp. normal

25-OH-vitamin D
- Vitamin D sufficiency
- Vitamin D deficiency

Causes:
- GI losses
- Nutritional
- Low sun exposure

Secondary Hyperparathyroidism:
- Malabsorption
- Vitamin D deficiency
- PHP 1,2
- VDDR 1,2

Hypomagnesemia

Hypoparathyroidism

Rickets

Causes:
- GI losses
- Nutritional
- Low sun exposure
Rickets

A-Decreased intake, Synthesis, Retention or Sequestration
- Maternal vitamin D deficiency, breastfeeding
- Reduced sun exposure
- Malabsorption: Celiac disease, CF, IDB
- Drugs: Anticonvulsants, Glucocorticoids
- Nephrotic syndrome
- Obesity

B-Metabolic Errors
- 25-Hydroxylase Deficiency (Vitamin D Dependent Rickets Type 1B)
- 1-α-Hydroxylase Deficiency (Vitamin D Dependent Rickets Type 1A)
- Vitamin D Receptor Mutations (Vitamin D Dependent Rickets Type 2A)
- HNRNPC mutations (Vitamin D Dependent Rickets Type 2B)

II- Calcium deficiency
A- Nutritional Deprivation
B- Hypercalciuria

III- Phosphate deficiency
A- Transcellular Shifts
B- Decreased intestinal absorption
C- Hyperphosphaturia (AR, AD, X-linked)
Repeated History & physical examination

- Received Vitamin D 400U until age 1 year
- Calcium level was normal until age 7 months
- Very low sun exposure
- Very low milk consumption
- Bow legs
- His parents both have low vitamin D levels and normal calcium, phosphorus and alkaline phosphatase levels

<table>
<thead>
<tr>
<th></th>
<th>mother</th>
<th>father</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>9.43</td>
<td>9.42</td>
<td>8.8-10.8 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.11</td>
<td>3.94</td>
<td>3.2-5.8 mg/dL</td>
</tr>
<tr>
<td>Vit D (25-OH)</td>
<td><strong>28.3</strong></td>
<td><strong>19.9</strong></td>
<td>75-250 nmol/L</td>
</tr>
</tbody>
</table>
Diagnosis:

- Hypocalcemic seizure Vs. Febrile convulsion
- Calciopenic Rickets
- Nutritional deficiency of calcium and vitamin D and low sun exposure.

Is that all?
Discussion

• Is this vitamin D level low enough to explain his hypocalcemia?

• Is there a genetic cause for abnormal metabolism of vitamin D?

• Differential Diagnosis:
  – Peudohypoparathyroidism type 1b?
  – Hypercalciuric Hypocalcemia?

• Maybe a combination of a few causes

Patient Vitamin D 26.4 nmol/l (10.5ng/ml)
Prevalence of Vitamin D deficiency in healthy subjects

- 25OHD < 50 nmol/l (20ng/ml)
  - In 42% of adolescents in USA

- 25OHD < 37.5 nmol/l (15ng/ml)
  - In 36% of black and 6% of white adolescents in USA
  - In 40-50% of European children and adolescents

Patient Vitamin D
26.4 nmol/l (10.5ng/ml)

Vitamin D deficiency is prevalent among healthy children and adolescents
Vitamin D status in Israel

In healthy subjects:
Vitamin D insufficiency in 78%
vitamin D deficiency in 27%

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. IMAJ 2010
## Vitamin D status in Israel

<table>
<thead>
<tr>
<th>Age/Vitamin D status</th>
<th>All (n=191)</th>
<th>Children Age&lt;5y (n=21)</th>
<th>Children 5&lt;Age&lt;20y (n=34)</th>
<th>Adults 20&lt;Age&lt;50y (n=121)</th>
<th>Older Adults Age&gt;50y (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D level (nmol/l) (mean±SD)</strong></td>
<td>57.25±25.2</td>
<td>71.5±33.8*</td>
<td>56.32±22.7</td>
<td>56.4±24.1</td>
<td>44.5±19.5</td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Prev. of vit D insufficiency (&lt;75nmol/l)</strong></td>
<td>149 (78%)</td>
<td>11 (52.4%)#</td>
<td>27 (79.4)</td>
<td>98 (80.1%)</td>
<td>13 (86.7%)</td>
<td>&lt;0.05#</td>
</tr>
<tr>
<td><strong>Prev. of vit D deficiency (&lt;37.5nmol/l)</strong></td>
<td>52 (27.2%)</td>
<td>4 (19%)</td>
<td>9 (26.5%)</td>
<td>33 (27.3%)</td>
<td>6 (40%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Vitamin D deficiency in 19% of healthy children < 5y*

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. *IMAJ* 2010
## Comparison of vitamin D status by ethnicity

<table>
<thead>
<tr>
<th>Ethnic origin/ Vitamin D status</th>
<th>Ashkenazi Jews (n=26)</th>
<th>Sephardic Jews (n=38)</th>
<th>Arabs (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D level (nmol/l)</strong></td>
<td>78.5±29.2</td>
<td>60.25±25.7</td>
<td>44±23.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(mean±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prev. of vit D insufficiency (&lt;75nmol/l)</strong></td>
<td>14 (53.8%)</td>
<td>29 (76.3%)</td>
<td>22 (84.6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Prev. of vit D deficiency (&lt;37.5nmol/l)</strong></td>
<td>3 (11.5%)</td>
<td>8 (21.1%)</td>
<td>12 (46.2%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Vitamin D deficiency in 46% of Arab population

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. *IMAJ* 2010
Recommendation for the classification of vitamin D status in children:

Global Consensus Recommendation on Prevention and Management of Nutritional Rickets.

Craig F. et al. JCEM 2016

- Sufficiency, >50 nmol/L (20 ng/ml)
- Insufficiency, 30–50 nmol/L (12-20 ng/ml)
- Deficiency, <30 nmol/L (<12 ng/ml)
Presentation of Vitamin D deficiency and Vitamin D levels

Table 1  Main presenting complaints among the 65 children with vitamin D deficiency

<table>
<thead>
<tr>
<th>Hypocalcaemic symptoms (n = 29)</th>
<th>n</th>
<th>No hypocalcaemic symptoms (n = 36)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsions</td>
<td>16</td>
<td>Incidental</td>
<td>11</td>
</tr>
<tr>
<td>Neuromuscular irritability</td>
<td>9</td>
<td>Bow legs</td>
<td>10</td>
</tr>
<tr>
<td>Apnoea</td>
<td>3</td>
<td>Bone pain</td>
<td>4</td>
</tr>
<tr>
<td>Stridor</td>
<td>1</td>
<td>Swollen joints</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone abnormality</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor delay</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short stature</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening family member</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2  A comparison of children presenting with and without hypocalcaemic symptoms

<table>
<thead>
<tr>
<th>Hypocalcaemic symptoms (n = 29)</th>
<th>No hypocalcaemic symptoms (n = 36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Ca^{2+}$ (mmol/l)</td>
<td>1.36 (0.84–2.08)</td>
<td>2.11 (1.32–2.49)</td>
</tr>
<tr>
<td>$PO_4$ (mmol/l)</td>
<td>1.57 (0.85–3.16)</td>
<td>0.87 (0.38–4.21)</td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>989 (266–4393)</td>
<td>1723 (356–8988)</td>
</tr>
<tr>
<td>25-OHD (nmol/l)</td>
<td>5.0 (2.1–14)</td>
<td>6.7 (2.7–14)</td>
</tr>
<tr>
<td>PTH (pmol/l)*</td>
<td>177 (22–760)</td>
<td>258 (21–640)</td>
</tr>
</tbody>
</table>

Results presented as median (range).
*Parathyroid hormone levels were only available for 18 and 14 children with and without hypocalcaemic symptoms, respectively (normal range: 1.1–6.8 pmol/l).

Hypothesis

The patient has only mild vitamin D deficiency, which is prevalent in healthy subjects and not low enough to explain his severe hypocalcemia.
In repeated questioning:

- He was drinking 1.5 liters of Coca Cola a day
- Coca cola replaced milk in his diet
“In addition to skin pigmentation and northern latitude, **low serum calcidiol** values have been attributed to meager consumption of milk and multivitamins, **large intake of phosphate containing soft drinks**, and increase in fat mass ...”

“Intestinal calcium absorption is influenced by vitamin D status...and the presence of **food inhibitors of calcium absorption** such as phytates, oxalates, or **phosphates (e.g. cola beverages)**.”
Phosphorus loads as a cause of hypocalcemia

- Formula with high phosphorus content (newborns)
- Phosphate containing enemas
- Phosphate containing oral laxatives
- TPN
Calcium and phosphate metabolism disorders secondary to consumption of soft drinks with phosphoric acid

Efrain Mazariegos Ramos et al, Boletín médico del Hospital Infantil de México, 1995
Consumption of soft drinks with phosphoric acid and hypocalcemia in children

- 57 children with hypocalcemia (ca<8.7 mg/dl)
- 171 controls (ca>8.7 mg/dl)
- Intake of at least 1.5 l/w of phosphate containing soft drinks was a risk factor for the development of hypocalcemia
- Negative correlation between calcium level and the amount of soft drink consumed
- In 17 children followed: Calcium levels rose and Phosphorus levels dropped after withdrawal of soft drink intake

Rat consuming phosphoric acid containing soft drinks developed

- Hypocalcemia
- Secondary hyperparathyroidism
- Decrease in vitamin D level
- Reduced BMD
Carbonated soft drinks consumption and BMD in humans

- Consumption of high amounts of carbonated soft drinks (mainly coca cola) leads to:
  - Decrease in BMD
  - Increase in bone fractures in adolescents and adults.

Mechanisms:
- High Phosphate content
- Caffeine content
- Low PH
- Displacement of milk consumption
Mechanisms by which Phosphorus loads can cause Hypocalcemia

- Inhibition of Calcium absorption

Effects of Hyperphosphatemia:
- Inhibition of bone resorption
- Inhibition of 1-\(\alpha\)-hydroxylase
- Formation of insoluble calcium phosphate precipitates
Calcium and Phosphorus content of various drinks: (mg/100ml)

<table>
<thead>
<tr>
<th></th>
<th>Cow’s milk</th>
<th>Infant formula</th>
<th>Human milk</th>
<th>Coca cola</th>
<th>Orange juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>114</td>
<td>54</td>
<td>33.8</td>
<td>0</td>
<td>3.38</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>87</td>
<td>30</td>
<td>13.5</td>
<td>17</td>
<td>3.38</td>
</tr>
<tr>
<td>Ca/P ratio</td>
<td>1.31</td>
<td>1.8</td>
<td>2.5</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Ca/P ratio is important
Conclusion

Considering this large intake of phosphorus in coca cola with almost no intake of calcium we assume that ingestion of large amount of **coca cola** was a major contributing factor for **hypocalcemia** in this child.
Follow Up:

**Patient Management:**

- Calcium Sandoz P.O. – 500 mg X 2/day
- Vitamin D (25OH)- 2000 U/day
- Stop completely consumption of coca cola
- Diet rich in dairy products and fish
- Controlled exposure to sunlight
Follow Up

<table>
<thead>
<tr>
<th></th>
<th>2.3Y</th>
<th>2.5y</th>
<th>2.7y</th>
<th>2.11y</th>
<th>Normal values</th>
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<tr>
<td>presentation</td>
<td>discharge</td>
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<tr>
<td>Calcium</td>
<td>6.17</td>
<td>9.57</td>
<td>9.96</td>
<td>10.28</td>
<td>10.8</td>
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<td>5.11</td>
<td>6.20</td>
<td>6.42</td>
<td>6.92</td>
</tr>
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<td>865</td>
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<td>323</td>
<td>331</td>
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<tr>
<td>Vit D (25-OH)</td>
<td>26.4</td>
<td>130.0</td>
<td>67.2</td>
<td>76.2</td>
<td></td>
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<td></td>
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<td>1-25 di-OH Vit D</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-0.6</td>
</tr>
</tbody>
</table>

Current therapy: Vitamin D3 – 400 U/day
X-rays before and after treatment

Before

After
Summary

• A child with hypocalcemic seizure and Calciopenic Rickets

• Causes for his hypocalcemia:
  – Vitamin D deficiency
  – Nutritional deficiency of calcium
  – Consumption of large amounts of coca cola

• Consumption of phosphate containing soft drinks in a risk factor for the development of hypocalcemia in children

• Consumption of phosphate containing soft drinks is related to decreased BMD in adolescents and adults
Take home message

• Anamnesis is still important...

• We should consider the hazardous effect of phosphate containing soft drinks on calcium metabolism in evaluation of a child with hypocalcemia

• This is another hazardous effect added to the list of known disadvantages of these drinks.
Thanks for listening
Discussion

**ORIGINAL ARTICLE**

**Presentation of vitamin D deficiency**

S Ladhani, L Srinivasan, C Buchanan, J Allgrove

*Arch Dis Child* 2004
## Discussion

### Symptomatic rickets in adolescence

H Narchi, M El Jamil, N Kulaylat

Arch Dis Child 2001

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Biochemical results at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum parameter</strong></td>
<td><strong>Normal values</strong></td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.2–2.7</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.1–1.8</td>
</tr>
<tr>
<td>Ca × P product (mmol²/l²)</td>
<td>3.3</td>
</tr>
<tr>
<td>Parathormone (pmol/l)</td>
<td>1.0–5.2</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>80–280</td>
</tr>
<tr>
<td><strong>25-hydroxyvitamin D (nmol/l)</strong></td>
<td>10–80</td>
</tr>
<tr>
<td>1,25-hydroxyvitamin D (pmol/l)</td>
<td>38–150</td>
</tr>
</tbody>
</table>
Hypotheses explaining the relationship between cola beverages consumption and impairment of bone and mineral metabolism

• High Phosphate content
• Caffeine content
• Low PH
• Displacement of milk consumption
<table>
<thead>
<tr>
<th>Stage</th>
<th>Plasma Ca++</th>
<th>Plasma PO₄</th>
<th>ALP</th>
<th>PTH</th>
<th>25(OH)-D</th>
<th>1,25(OH)₂-D</th>
<th>Radiograph Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>N/↓</td>
<td>N/↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Moderate</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓↓</td>
<td>↑</td>
<td>Rachitic changes +</td>
</tr>
<tr>
<td>Severe</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
<td>↑/N/↓</td>
<td>Rachitic changes + +</td>
</tr>
</tbody>
</table>

N indicates normal; ↑, increase; ↓, decrease. + mild changes; ++ moderate to severe changes


Biochemical Manifestation of Different Stages of Vitamin D Deficiency:

## Follow Up

<table>
<thead>
<tr>
<th></th>
<th>2.3Y</th>
<th>2.5y</th>
<th>2.7y</th>
<th>2.11y</th>
<th>3.1y</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>presentstion discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>6.17</td>
<td>9.57</td>
<td>9.96</td>
<td>10.28</td>
<td>10.8</td>
<td>9.84</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5.16</td>
<td>5.11</td>
<td>6.20</td>
<td>6.42</td>
<td>6.92</td>
<td>5.55</td>
</tr>
<tr>
<td>Alk. Phos.</td>
<td>865</td>
<td>698</td>
<td>323</td>
<td>331</td>
<td>331</td>
<td>350</td>
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<tr>
<td>Magnesium</td>
<td>2.22</td>
<td>2.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vit D (25-OH)</td>
<td>26.4</td>
<td>130.0</td>
<td>67.2</td>
<td>76.2</td>
<td>53.2</td>
<td>75-250 nmol/L*</td>
</tr>
<tr>
<td>1-25 di-OH Vit D</td>
<td>357.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.0-72.0 pg/mL</td>
</tr>
<tr>
<td>PTH</td>
<td>273.5</td>
<td>341.1</td>
<td>83.9</td>
<td>44.9</td>
<td>172.7</td>
<td>3.8-5.4 g/dL</td>
</tr>
<tr>
<td>U ca/creatinine</td>
<td>0.389*</td>
<td></td>
<td></td>
<td>1.64</td>
<td></td>
<td>0-0.6</td>
</tr>
<tr>
<td>TRP</td>
<td></td>
<td></td>
<td></td>
<td>91.5%</td>
<td></td>
<td>&gt;80%</td>
</tr>
<tr>
<td>TmP/GFR</td>
<td>5.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8-4.4 mg/dl</td>
</tr>
</tbody>
</table>

*on IV calcium therapy
Hypocalcemia

- Mg++
  - Low
  - Normal
- PTH
  - Elevated
  - Low/inapp. normal
- 25-OH-vitamin D
  - Vitamin D sufficiency
  - Vitamin D deficiency

Secondary Hyperparathyroidism:
- Malabsorption
- Vitamin D deficiency
- PHP 1,2
- VDDR 1,2

Hypomagnesemia

Hypoparathyroidism

Causes:
- GI losses
- Nutritional
- Low sun exposure
# Vitamin D status in Israel

<table>
<thead>
<tr>
<th>Age/ Vitamin D status</th>
<th>All (n=191)</th>
<th>Children Age&lt;5y (n=21)</th>
<th>Children 5&lt;Age&lt;20y (n=34)</th>
<th>Adults 20&lt;Age&lt;50y (n=121)</th>
<th>Older Adults Age&gt;50y (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D level</strong> (nmol/l) (mean±SD)</td>
<td>57.25±25.2</td>
<td>71.5±33.8*</td>
<td>56.32±22.7</td>
<td>56.4±24.1</td>
<td>44.5±19.5</td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Prev. of vit D insufficiency</strong> (&lt;75nmol/l)</td>
<td>149 (78%)</td>
<td>11 (52.4%)#</td>
<td>27 (79.4)</td>
<td>98 (80.1%)</td>
<td>13 (86.7%)</td>
<td>&lt;0.05#</td>
</tr>
<tr>
<td><strong>Prev. of vit D deficiency</strong> (&lt;37.5nmol/l)</td>
<td>52 (27.2%)</td>
<td>4 (19%)</td>
<td>9 (26.5%)</td>
<td>33 (27.3%)</td>
<td>6 (40%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. *IMAJ* 2010
Comparison of vitamin D status by ethnicity

<table>
<thead>
<tr>
<th>Ethnic origin/Vitamin D status</th>
<th>Ashkenazi Jews (n=26)</th>
<th>Sephardic Jews (n=38)</th>
<th>Arabs (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D level</strong></td>
<td>78.5±29.2</td>
<td>60.25±25.7</td>
<td>44±23.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(nmol/l) (mean±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prev. of vit D insufficiency</strong></td>
<td>14 (53.8%)</td>
<td>29 (76.3%)</td>
<td>22 (84.6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(&lt;75nmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prev. of vit D deficiency</strong></td>
<td>3 (11.5%)</td>
<td>8 (21.1%)</td>
<td>12 (46.2%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(&lt;37.5nmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. *IMAJ* 2010
Prevalence of Vitamin D deficiency in healthy subjects

• 307 healthy urban adolescents in northeastern US
  – 25OHD < 50 nmol/l In 42%
  – 25OHD < 37.5 nmol/l In 36% of black, 22% of hispanic, and 6% of whites subjects

• 25OHD < 32.5 nmol/l: in up to 40-50% of European children and adolescents

Vitamin D units: 1ng/ml = 2.5 nmol/l

Vitamin D -26.4 nmol/l
In healthy subjects:
Vitamin D insufficiency in 78%
Vitamin D deficiency in 27%

In healthy children <5 yrs
Vitamin D deficiency in 19%

In healthy Israeli Arabs
Vitamin D deficiency in 46%

Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis. Oren Y. et al. IMAJ 2010
Calcium and phosphate metabolism disorders secondary to consumption of soft drinks with phosphoric acid
Efrain Mazariegos Ramos et al, Boletín médico del Hospital Infantil de México, 1995

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Presentation</th>
<th>Ca (mg/dl)</th>
<th>P (mg/dl)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 y</td>
<td>M</td>
<td>Night fears</td>
<td>7.1</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10.7 y</td>
<td>F</td>
<td>Convulsions</td>
<td>7.0</td>
<td>5.7</td>
<td>Phenytoin Calcitriol 0.25mcg/d</td>
</tr>
<tr>
<td>3</td>
<td>8m</td>
<td>M</td>
<td>Breath Holding spells</td>
<td>7.2</td>
<td>7.2</td>
<td>Phenytoin Calcitriol 0.25mcg/2d</td>
</tr>
<tr>
<td>4</td>
<td>11y</td>
<td>M</td>
<td>Convulsions</td>
<td>7.4</td>
<td>5.1</td>
<td>Calcitriol 0.25mcg/d</td>
</tr>
<tr>
<td>5</td>
<td>3.8y</td>
<td>M</td>
<td>Convulsions</td>
<td>8.0</td>
<td>7.2</td>
<td>Calcitriol 0.25mcg/d</td>
</tr>
</tbody>
</table>
Consumption of soft drinks with phosphoric acid and hypocalcemia in children


<table>
<thead>
<tr>
<th></th>
<th>Case (n=57)</th>
<th>Control (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)*</td>
<td>29/28</td>
<td>87/84</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>67.5 ± 29.3 (18-142)</td>
<td>67.5 ± 29.0 (18-142)</td>
</tr>
<tr>
<td>Soft drink use (bottles/wk)‡</td>
<td>6 ± 8 (0-21)</td>
<td>2 ± 3 (0-9)</td>
</tr>
<tr>
<td>Ca (mmol/L; mg/dl)</td>
<td>2.1 ± 0.1 (1.7-2.1); 8.3 ± 0.3 (7.0-8.7)</td>
<td>2.4 ± 0.1 (2.2-2.9); 9.2 ± 0.6 (8.8-11.8)</td>
</tr>
<tr>
<td>P (mmol/L; mg/dl)</td>
<td>1.7 ± 0.4 (1.2-3.0); 5.3 ± 1.3 (3.6-9.4)</td>
<td>1.6 ± 0.3 (0.7-2.6); 5.0 ± 1.0 (2.3-7.9)</td>
</tr>
<tr>
<td>Albumin (μmol/L; gm/dl)</td>
<td>517 ± 57 (356-620); 4.5 ± 0.5 (3.1-5.4)</td>
<td>528 ± 35 (414-666); 4.6 ± 0.3 (3.6-5.8)</td>
</tr>
</tbody>
</table>

>4 bottles (375ml)/w        38 (66.7%)                         48 (28%)  
≥ 1 seizures                4 (7%)                              1 (0.6%)  
Cramps                      13 (23%)                            8 (5%)
X-rays before and after treatment
X-rays before and after treatment
Hypotheses explaining the relationship between cola beverages consumption and impairment of bone and mineral metabolism

- High Phosphate content
- Caffeine content
- Low PH
- Displacement of milk consumption
Conclusion

• We should consider the **hazardous effect of phosphate containing soft drinks on calcium metabolism** in evaluation of a child with hypocalcemia

• This is another hazardous effect added to the list of known disadvantages of these drinks.
$\text{Ca}^{++} \downarrow$

$\text{PTH} \uparrow$

$\text{1,25(OH)}_2\text{D} \uparrow$

$\text{1 \alpha \ Hydroxylase} \uparrow$

$25(\text{OH})\text{D} \rightarrow 1,25(\text{OH})_2\text{D} \rightarrow 1,25(\text{OH})_2\text{D} \uparrow$

$\uparrow \text{Ca absorption}$

$\uparrow \text{Ca reabsorption}$

$\uparrow \text{Phosphate excretion}$

$\uparrow \text{Bone resoprtion}$
Causes of Hypocalcemia

I- Neonatal

A Maternal disorders
- Diabetes mellitus
- Toxemia of pregnancy
- Vitamin D def.
- Use of anticonvulsants
- Hyperparathyroidism

A Neonatal disorders
- LBW, prematurity, IUGR
- Asphyxia, sepsis, critical illness
- Hyperbilirubinemia, phototherapy, exchange transfusion
- Acute/chronic renal failure
- Nutrients/medications: high phosphate intake, bicarbonate, phytates, anticonvulsants

II- Hypoparathyroidism

A congenital
- Transient neonatal
- Congenital hypoparathyroidism
  - Familial isolated (AR, AD, X linked)
  - DiGeorge
  - Syndromic
- Insensitivity to PTH
  - Bloomstrand chondrodysplasia (PTHR1)
  - Pseudohypoparathyroidism (PHP)-IA,IB,IC,II
  - Hypomagnesemia

B Acquired
- Autoimmune polyglandular syndrome type 1
- Post surgical, radiation destruction
- Infiltrative (Hemochromatosis, Wilson)

III- Vitamin D deficiency

IV- Others

A calcium deficiency – nutritional
B Hypomagnesemia
C Hyperphosphatemia
Prevalence of Vitamin D deficiency in healthy subjects

• 25OHD < 37.5 nmol/l (15ng/ml)
  ▪ In 40-50% of European children and adolescents

In Israel:

vitamin D deficiency in:
• 27% of healthy subjects
• 19% of children <5 yrs
• 46% of Israeli Arabs

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