Vitamin D in pregnancy and early life -implications for the mother and child

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2006

One Vitamin That Can Save Your Life

Reader's Digest

Great Bargains 2003

PAY LESS

Get Everything

Why You Need This Healing Vitamin

Rethinking Race, Racism & Fairness

The West Nile Epidemic • Survival at Sea

Humor in Uniform: Bob Hope’s 100th Birthday
Vitamin D

- Nutrient and pro-hormone

- Vitamin D receptors found from most tissues and organs of the body
  - Bone
  - Brain
  - Breast
  - Deciduas
  - Heart
  - Immune cells
  - Placenta
  - Pancreas
  - Prostate
  - Etc.
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Proposed health effects of vitamin D

**Regulation of calcium metabolism**
- Rickets, Osteomalacia
- Osteoporosis
- Fractures

**Immunomodulatory effects**
- Type 1 diabetes
- Multiple Sclerosis
- Psoriasis
- Arthritis
- Inflammatory Bowel disease
- Pre-eclampsia
- Allergic diseases

**Cardiovascular effects**
- Hypertension
- Metabolic syndrome
- CVD
- Heart failure

**Cell growth and regulation**
- Cancer risk
  (prostate, colon, breast etc.)

Holick M. NEJM 2007
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Holick M. NEJM 2007
Immunological link between vitamin D and miscarriage/pregnancy complications?

**Pregnancy as an immunological challenge**
- Fetus is an allogenic tissue graft carrying paternally derived antigens.
- Immunological adaptation by a sift towards a domination by the T helper type 2 (Th2) cytokine response required for the maintenance of normal pregnancy
  - Th1 type reaction in the placenta correlated with spontaneous preterm delivery and miscarriage, possible role in pre-eclampsia

**Vitamin D - Immunomodulatory properties**
- Active vitamin D attenuates Th1-mediated immune response
  - Reduces secretion of INF-γ, IL-2, IL-12
- Affects dendritic cell maturation
- Affects regulatory T-cell activity

**Vitamin D may be able to prevent the immune maladaptation and loss of tolerance in pre-eclampsia / miscarriage?**

Hyppönen. NutrRev,2005
NORMAL PREGNANCY

- Th2 domination

- Expressed in macrophages, placenta and deciduas.

- Levels increased from early pregnancy.

- Expressed in placenta and deciduas.

- Required for normal reproduction.

PRE-ECLAMPSIA

- Th1 overexpression

- Altered expression/activity in pre-eclampsia?

- Pre-eclampsia associated with genetic variations in VDR?

- Levels decreased compared to normal pregnant controls.

- Expression and activity is restricted

- Levels decreased

- Incidence mirrors seasonal variations in vitamin D status

Vitamin D intake

Vitamin D receptor (VDR)

1α-hydroxylase

25(OH)D

1,25(OH)_2D

Immunological tolerance

Immunomodulation

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Vitamin D intake

PRE-ECLAMPSIA

Impaired

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Hyppönen. NutrRev, 2005
Bodnar et al. Maternal vitamin D deficiency increases the risk of preeclampsia. JCEM 2007
- Nested case-control study with 55 cases and 219 controls
- 25(OH)D concentrations measured by 16wk, pre-eclampsia onset after 20wks.
  - 25(OH)D concentrations lower in pre-eclamptic women compared to controls (45nmol/l vs. 53nmol/l, p=0.01)
  - 2-fold increase in pre-eclampsia risk for 50nmol/l increase in 25(OH)D
  - 25(OH)D concentrations lower in the offspring to pre-eclamptic women compared to offspring of controls (39nmol/l vs. 50 nmol/l, p=0.001)

Haugen et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology 2009
- Norwegian Mother and Child Cohort, 23,423 nulliparous pregnant women (1267 with preeclampsia)
- Questionnaire Information vitamin D supplementation (week 15) and dietary intake (week 22)
- Pregnancy outcomes were obtained from the Medical Birth Registry.
  - Total vitamin D intake (15-20 µg/d vs. <5µg/d) associated with reduced pre-eclampsia risk
    (OR 0.76, 95%CI 0.60-0.95).
  - Vitamin D supplementation (vs. no supplements) associated with reduced pre-eclampsia risk
    (OR 0.73, 95%CI 0.58-0.92).
  - No association between vitamin D intake from food and preeclampsia
Does early-life vitamin D status or intake have long-term influences on immunological diseases?

- Programming of the immune system, in particular related to tolerance development, starts before birth and stays under close control of the maternal immune system
  - Pre- and postnatal period important ‘window of opportunity’ for immune programming
  - Controlled by gene-environment interaction, epigenetic mechanisms

- Evidence for epigenetic regulation of genes in the vitamin D pathway
  - Placenta specific methylation of 24-hydroxylase
  - Transcriptional regulation of the CYP27B1 gene mediated by epigenetic modifications
Vitamin D and type 1 diabetes

TYPE 1 DIABETES
• Chronic autoimmune disease, multifactorial etiology with both genetic predisposition and exposure to environmental risk factors required

• Long latency from initiation to disease onset

• Insulin secreting beta cells destroyed in a T-cell dependent process

• Polarization towards Th1 up-regulation is believed central to the pathogenesis

Vitamin D may be able to disrupt both the initiation and progression of the T-cell mediated pathogenesis of Type 1 diabetes?
Stene et al. Diabetologia, 2000
- Norwegian case-control study, 85 cases / 1071 control children
  - Maternal cod liver oil supplementation during pregnancy associated with a reduced diabetes risk in the offspring (OR 0.30, 95%CI 0.12-0.75)
  - Results inconclusive on the effect of infants cod liver oil intake or vitamin D supplementation

Fronzak et al. Diabetes Care 2003
- 233 children followed up for 4y, 16 developed insulin autoantibodies
  - Maternal intake of vitamin D via food associated with decreased risk of IA antibodies (HR 0.37, 95%CI 0.17, 0.78)

Brekke and Ludvigsson, Pediatr Diabetes 2007
- Follow-up of 8695 children up to 1y for seroconversion to positivity for diabetes specific autoantibodies (n=774). (For 2.5y, 7766 and 774, respectively)
  - Use of vitamin-D supplements during pregnancy associated with reduced diabetes-related autoimmunity at 1y (OR 0.71, 95%CI 0.52-0.96) but not at 2.5y.
* All pregnant mothers with expected date of delivery in 1966 in two most northern provinces of Finland (n=12,058)

* Information on vitamin D supplementation (frequency, dose) and suspected rickets collected at 1 year of age (n=10,366)

*****Dose recommendation 2000 IU/day (50µg/day)*****

- Follow-up for Type 1 diabetes to age 31 through linkage to Central Drug Register with further ascertainment of cases diagnosed at age 20 or older using hospital discharge register and/or medical files
  - 81 cases (total n=10,366)
Incidence of Type 1 diabetes by FREQUENCY of vitamin D supplementation

Adjusted for: sex, neonatal, social and anthropometrica indicators

Hyppönen et al. Lancet, 2001
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Hyppönen et al. Lancet, 2001
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Incidence of Type 1 diabetes by DOSE of vitamin D supplementation

Restricted to children receiving vitamin D regularly

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Incidence of Type 1 diabetes by DOSE of vitamin D supplementation

Restricted to children receiving vitamin D regularly

Adjusted for: sex, neonatal, social and anthropometric indicators

Hyppönen et al. Lancet, 2001
Incidence of Type 1 diabetes by suspected RICKETS

RR = 3.0
p<0.05

Adjusted for:
increased dose, sex, neonatal, social, and anthropometric indicators

Hyppönen et al. Lancet, 2001
Long-term effects of infant vitamin D supplementation on the risk of immune mediated diseases: Th1/Th2 paradigm
Long-term effects of infant vitamin D supplementation on the risk of immune mediated diseases: Th1/Th2 paradigm

Type 1 diabetes ↓
Pre-eclampsia ↓
<table>
<thead>
<tr>
<th>Frequency of vitamin D supplementation</th>
<th>number</th>
<th>% (cases)</th>
<th>OR (95% CI)</th>
<th>Adjusted (^a) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregularly/none</td>
<td>339</td>
<td>3.8 (13)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Regularly</td>
<td>2630</td>
<td>2.1 (55)</td>
<td>0.54 (0.29, 0.99)</td>
<td>0.49 (0.26, 0.92)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of vitamin D(^b)</th>
<th>number</th>
<th>% (cases)</th>
<th>OR (95% CI)</th>
<th>Adjusted (^a) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 IU per day</td>
<td>2499</td>
<td>2.1 (53)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt; 2000 IU per day</td>
<td>120</td>
<td>1.7 (2)</td>
<td>0.78 (0.19, 3.26)</td>
<td>0.81 (0.18, 3.55)</td>
</tr>
</tbody>
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Prevalence and risk of pre-eclampsia by vitamin D supplementation in infancy - Northern Finland Birth Cohort 1966

Hyppönen et al. EJCN 2007
Long-term effects of infant vitamin D supplementation on the risk of immune mediated diseases: Th1/Th2 paradigm
Long-term effects of infant vitamin D supplementation on the risk of immune mediated diseases: Th1/Th2 paradigm

- Vitamin D
- Allergy ↑
- Th2

- Type 1 diabetes ↓
- Pre-eclampsia ↓
Prevalence of allergic conditions by FREQUENCY of vitamin D supplementation

**p<0.001, * p=0.05**

Hyppönen et al. ANYAS, 2004
Prevalence of allergic conditions by 
DOSE* of vitamin D supplementation

* Restricted to infants receiving vitamin D regularly

Hyppönen et al. ANYAS, 2004
Support for increases in allergy/asthma by vitamin D...

**Gale et al. EJCN 2007**

Higher maternal vitamin D status during pregnancy associated with...
...3-fold risk (95%CI 1.2-9) of visible eczema at 9 months
...over 5-fold risk (95%CI 1.1-27) of reported asthma at 9 years

**Hughes et al. Pediatr Allergy & Immunol 2010**

In an Australian study...
..cod liver oil supplementation in childhood associated with hayfever/asthma
..greater wintertime sun exposure in childhood associated with hayfever
Serum IgE by variations in 25(OH)D
-geometric mean, standardized by sex and season

Hyppönen et al. Allergy, 2009
... but what about all this??

Is vitamin D deficiency to blame for the asthma epidemic?
Litonjua & Weiss, J Allergy Clin Immunol 2007

“..using data from the two birth cohorts with maternal vitamin D assessments, we estimate that the population attributable risk for asthma incidence caused by vitamin D deficiency in pregnancy is about 40% of all cases.”

Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Camargo et al. AJCN 2007

1194 mother-child pairs: Compared with mothers in the lowest quartile of daily intake (median: 356 IU), those in the highest quartile (724 IU) had a lower risk of having a child with recurrent wheeze [OR: 0.39; 95% CI: 0.25, 0.62; P for trend < 0.001].


1212 children: maternal total vitamin D intake (highest: 275IU/day vs lowest: 77IU/day quintiles) conferred lower risks for ever wheeze [OR: 0.48; 95% CI: 0.25, 0.91], wheeze in the previous year (OR: 0.35; 95% CI: 0.15, 0.83), and persistent wheeze (OR: 0.33; 95% CI: 0.11, 0.98) in child at 5y.
Serum IgE by variations in 25(OH)D
- geometric mean, standardized by sex and season

Hyppönen et al. Allergy, 2009
Airway eosinophilia - a key pathophysiological feature of asthma - was also reduced, possibly suggesting beneficial influences through a reduced inflammatory response.

Vitamin D status and prevalence of respiratory infections in the 1958BC

Berry et al. BJN 2011, in press
Active vitamin D (i.e. 1,25(OH)$_2$D)…

- leads to a **general reduction in inflammation**, which together with direct anti-proliferative effects in human airway smooth muscle cells (through inhibition of matrix metallo-proteinases) is believed to be instrumental for explaining the observed reductions in asthma risk.

- influences **barrier integrity**, which could protect against the direct influence of harmful pathogens.

- reduces **MHC II antigen expression** on the cell membrane surface and induces macrophages and epithelial cells to produce cathelicidin, a peptide involved in antimicrobial action.

…in addition to affecting regulatory T cell activity, and the balance between Th1 and Th2 type immunological responses.
Summary

- Vitamin D is a powerful immunomodulator, which can have long term influences on immunological disease such as diabetes and allergy risk
  - Evidence accumulating for beneficial effects in infections/inflammation

- Hypovitaminosis D short of deficiency may have important implications for
  - the maintenance of normal pregnancy
  - long-term implications for offspring health.
Public health message: Avoid vitamin D deficiency!