Vitamin D deficiency, the novel disease??
An effort to focus on the evidence contrary to the tendency for generalized substitution

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Sunlight: UV B — 270-290 nm
10 minutes of summer sun over the weekend without sunblock makes ~10,000 IU of Vitamin D

Diet:
- 20%
  - Vitamin D2
  - Vitamin D3

7-Dehydrocholesterol → Pre Vitamin D3 → Vitamin D

Liver → 25 Hydroxyvitamin D → 25 Hydroxylase → CYP3A4

Skin → 80%
Vitamin-D UV dose (kJ/m²)
Vitamin-D UV dose (kJ/m²)

SCIAMACHY - KNMI/ESA

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21 December 2006

Clear-sky
Synthesis, metabolism, biological actions
The role of parathyroid hormone and vitamin D in the metabolism of calcium. 1,25(OH)2D3, 1,25 dihydroxyvitamin D3; P-, phosphate; PTH, parathyroid hormone. (Modified from Boon NA, Colledge NR, Walker BR, Hunter JAA [eds]: Davidson’s Principles & Practice of Medicine, 20th ed. Edinburgh, Churchill Livingstone, 2006, p. 772.)
<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>(ng/dL)</th>
<th>(nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient (high risk)</td>
<td>&lt;20</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Insufficient (moderate risk)</td>
<td>20-29</td>
<td>50-72</td>
</tr>
<tr>
<td>Adequate (low risk)</td>
<td>30 or higher</td>
<td>73 or higher</td>
</tr>
</tbody>
</table>

Serum vitamin D test results (25-Hydroxyvitamin D) are shown in these two units.
<table>
<thead>
<tr>
<th>Tissue VDR localisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System</td>
</tr>
<tr>
<td>- T and B cells</td>
</tr>
<tr>
<td>- macrophages</td>
</tr>
<tr>
<td>- neutrophils</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>- endothelium</td>
</tr>
<tr>
<td>- smooth muscle cells</td>
</tr>
<tr>
<td>- myocardium</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>- parathyroids</td>
</tr>
<tr>
<td>- β cell pancreas</td>
</tr>
<tr>
<td>- thyroid</td>
</tr>
<tr>
<td>Other Tissues</td>
</tr>
<tr>
<td>- exocrine</td>
</tr>
<tr>
<td>- neural</td>
</tr>
<tr>
<td>- reproductive</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>- podocytes</td>
</tr>
<tr>
<td>- mesangial cells</td>
</tr>
<tr>
<td>- glomerulli</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>- osteoblasts</td>
</tr>
<tr>
<td>- osteocytes</td>
</tr>
<tr>
<td>- muscle cells</td>
</tr>
<tr>
<td>Connective tissue</td>
</tr>
<tr>
<td>- fibroblasts</td>
</tr>
<tr>
<td>- interstitial cells</td>
</tr>
<tr>
<td>Other Systems</td>
</tr>
<tr>
<td>- epidermis</td>
</tr>
<tr>
<td>- liver</td>
</tr>
<tr>
<td>- gastrointestinal</td>
</tr>
<tr>
<td>- respiratory</td>
</tr>
</tbody>
</table>
Endocrine and paracrine actions of 1,25-dihydroxyvitamin D (1,25[OH]2D)
Vitamin D Deficiency

CAUSES
- Sun
- Sunscreen
- Melanin
- Latitude
- Winter
- Medications & Supplements
  - Antiseizure Medications
  - Glucocorticoids
  - Rifampin
  - HAART
  - St John's Wart
- Malabsorption
  - Crohn Disease
  - Whipple Disease
  - Cystic Fibrosis
  - Celiac Disease
  - Liver Disease

VITAMIN D DEFICIENCY
- Schizophrenia
- Depression
- Infections
  - URI
  - TB
- Asthma & Wheezing Diseases
- HBP
- CHD
- AODM
- Syndrome X
- Autoimmune Diseases
  - Type 1 Diabetes
  - MS
  - Crohn Disease
  - RA
- Muscle weakness
- Muscle aches
- Osteoarthritis
- Osteoporosis
- Osteomalacia (Bone Pain)
- Rickets
- Cancer
  - Breast
  - Colon
  - Prostate
  - Pancreas
  - etc.
Diabetes: A global emergency

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

North America and Caribbean
- 2015: 44.3 million
- 2040: 60.5 million

Europe
- 2015: 59.8 million
- 2040: 71.1 million

Middle East and North Africa
- 2015: 35.4 million
- 2040: 72.1 million

South and Central America
- 2015: 29.6 million
- 2040: 48.8 million

Africa
- 2015: 14.2 million
- 2040: 34.2 million

Western Pacific
- 2015: 153.2 million
- 2040: 214.8 million

South East Asia
- 2015: 78.3 million
- 2040: 140.2 million
Diabetes around the world

The prevalence of diabetes

2015

One in 11 adults has diabetes

2040

One in 10 adults will have diabetes
Type 2 DM: pathogenesis

Ominous Octet

- Impaired insulin secretion
- Increased glucagon secretion
- Decreased incretin effect
- Increased lipolysis
- Increased glucose reabsorption
- Increased hepatic glucose production
- Neurotransmitter dysfunction
- Decreased glucose uptake

Figure 1. Potential mechanisms by which vitamin D may influence T2DM. Vitamin D could influence T2DM through several pathways distinguished into three major mechanisms: (1) Stimulates insulin secretion by its interaction with VDRE localized in the promoter region of insulin gene, or stimulates indirectly the secretion of insulin granules through the regulation of intracellular calcium concentration. (2) Stimulates insulin sensitivity through the regulation of IRS expression in target cells and the activation of PPAR-δ in skeletal muscle and adipose tissues which is involved in fatty acid metabolism. Therefore 25(OH)D₃ regulates the correct function of skeletal muscle and reduces inflammation and changes adipokine secretion in adipose tissue. Indirectly, 25(OH)D₃ inhibits the RAAS, with an improvement of insulin resistance. (3) Regulates systemic inflammation through an inhibition of dendritic cells differentiation and proinflammatory cytokines, such as TNFα, IL6, IL1, IL2, and IFNγ. Thus results in an indirect shift in T cells polarization from T helper (Th) 1 to Th2 and in a reduction of macrophage infiltration. Abbreviation: 1αOHase: 1α-hydroxylase; Ca²⁺: calcium; DC: Dendritic Cell; ER: Endoplasmatic Reticulum; IP₃: inositol 1,4,5-trisphosphate; IR: insulin receptor; PKA: Protein Kinase A; PKC: Protein Kinase C; PPAR-δ: peroxisome proliferator-activated receptor gamma; RAAS: Renin-Angiotensin-Aldosteron system; ROS: reactive oxygen species; RXR: Retinoid X Receptor; Th: T helper lymphocyte; VDR: Vitamin D Receptor; VDRE: vitamin D responsive element.
Figure 2. Metabolic pathway of calcium and vitamin D on glucose metabolism. 25(OH)2D3 may modulates the increase of intracellular calcium level by the activation of two different signaling pathways mediated by two different protein kinases; PKA and PKC. The PKA mediates the phosphorylation of different proteins, including the L-type voltage-dependent calcium channels and proteins necessary for the exocytotic mechanism. 1,25(OH)2D3 activates the PLC, which cleaves PIP2 into IP3, involved in calcium release from the endoplasmic reticulum, and DAG that mediates the activation of the PKC. The PKC phosphorylates the KATP channels and the L-type voltage-dependent calcium channels causing the depolarization of the cytoplasmic membrane and the opening of the T-type voltage-dependent. These events increase intracellular calcium. The PKC also mobilizes the secretory vesicles. The increase of intracellular calcium concentration lead to the activation of CAMKII, a protein localized at the insulin secretory granules, which promotes the phosphorylation of several proteins involved in the mobilization of insulin granules resulting in exocytosis. Therefore, the increased of intracellular calcium level activates also the insulin gene expression via CREB. Furthermore, 1,25(OH)2D3 also regulates the expression of calbindin-D28k, a cytosolic calcium-binding protein, which stimulates insulin secretion by regulating intracellular calcium diffusion. Finally, the increased calcium level in muscle cells enhanced the recruitment of GLUT4 to the cell membrane, resulting in a decrease of insulin resistance. Abbreviation: 1αOHase: 1-α-hydroxylase; Ca2+: calcium; CAMKII: calcium-calmodulin-dependent protein kinase II; CREB: Calcium Responsive Element Binding protein; DAG: diacylglycerol; ER: Endoplasmic Reticulum; GLUT4: Glucose transporter type 4; IP3: inositol 1,4,5-trisphosphate; KATP channels: ATP-sensitive potassium channel; IP3: phosphoinosidites; PKA: Protein Kinase A; PKC: Protein Kinase C (PKC); PLC: phospholipase C.
Main clinical points-questions-
T2DM???

Does vitamin D deficiency predispose to DM?

Does vitamin D substitution prevent DM?

Does vitamin D substitution ameliorate glycemic control?
Men had higher serum vitamin D concentrations than women and showed a reduced risk of type 2 diabetes in their highest vitamin D quartile. The relative odds between the highest and lowest quartiles was 0.28 (95% confidence interval = 0.10-0.81) in men and 1.14 (0.60-2.17) in women after adjustment for smoking, body mass index, physical activity, and education. Men in the highest quartile of serum vitamin D had an 82% lower risk compared with those in the lowest quartile after adjustment for body mass index, physical activity, smoking, and education.

Knekt: Epidemiology, Volume 19(5).September 2008.666-671
Nested case-control study conducted among 608 women with newly diagnosed type 2 diabetes and 559 control subjects in the Nurses' Health Study, Association between baseline plasma 25-OHD concentration and risk of incident diabetes. Higher levels of plasma 25-OHD were associated with a lower risk for type 2 diabetes. The odds ratio for incident type 2 diabetes in the top (median 25-OHD, 33.4 ng/ml) versus the bottom (median 25-OHD, 14.4 ng/ml) quartile was 0.52 (95% CI 0.33–0.83). The associations were consistent across subgroups of baseline BMI, age, and calcium intake.

Pittas AG et al, Diabetes Care, 33(9) 2010
Adjusted relative risk of incident type 2 DM in the Nurses Health Study by calcium and vitamin D intake (52)
Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis

Parker J et al, Maturitas, 2009
Factors Contributing to Low Vitamin D Levels in Diabetes

<table>
<thead>
<tr>
<th>Dietary intake</th>
<th>Limited intake of foods high in vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun Exposure</td>
<td>Lack of outdoor physical activity due to possible fatigue, obesity, and/or mobility issues</td>
</tr>
<tr>
<td>Obesity</td>
<td>More vitamin D is stored in the fatty tissues and less is biologically active in the serum</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>Less biologically active vitamin D since conversion to the active form occurs in the kidneys</td>
</tr>
<tr>
<td>Genetic variations</td>
<td>Polymorphisms of vitamin D binding protein Polymorphisms of CYP2R1 gene (which is necessary to catalyze the formation of the main circulating vitamin D metabolite)</td>
</tr>
</tbody>
</table>

*Obesity is associated with inflammation, but low levels of vitamin D are also associated with inflammation. Cytokines and other inflammatory agents have been linked to beta cell damage which then impairs insulin synthesis and secretion.*

Penckofer et al. 2008
Does vitamin D deficiency predispose to DM?

Does vitamin D substitution prevent DM?

Does vitamin D substitution ameliorate glycemic control?
A total of 10 randomized controlled trials were included. Vitamin D did not significantly improve homeostatic model assessment of insulin resistance
Eight studies, with 1093 subjects (549 subjects in vitamin D and 544 subjects in control groups), contributed data on the effect of vitamin D supplementation on 2-h plasma glucose after OGTT. Again, vitamin D supplementation failed to show a significant effect on 2-h plasma glucose after OGTT.
Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change in fasting plasma glucose (mmol/l) for vitamin D supplementation and control.

The effect of vitamin D supplementation based on baseline 25(OH)D was inconclusive.
Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change of HbA$_{1c}$ (mmol/mol) for vitamin D supplementation and control.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Mean</th>
<th>Treatment SD</th>
<th>Treatment Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorde 2010</td>
<td>1.09</td>
<td>3.28</td>
<td>34</td>
<td>1.09</td>
<td>2.19</td>
<td>31</td>
<td>11.8%</td>
<td>0.00 [-1.35, 1.35]</td>
</tr>
<tr>
<td>Mitri (D vs Plb) 2011</td>
<td>0.87</td>
<td>2.62</td>
<td>23</td>
<td>1.97</td>
<td>2.19</td>
<td>12</td>
<td>9.5%</td>
<td>-1.10 [-2.74, 0.54]</td>
</tr>
<tr>
<td>Mitri (DCA vs Ca) 2011</td>
<td>0.55</td>
<td>2.62</td>
<td>12</td>
<td>0.96</td>
<td>2.51</td>
<td>22</td>
<td>8.4%</td>
<td>-0.43 [-2.25, 1.39]</td>
</tr>
<tr>
<td>Mitri (DCA vs Plb) 2011</td>
<td>0.55</td>
<td>2.62</td>
<td>11</td>
<td>1.97</td>
<td>2.19</td>
<td>12</td>
<td>7.5%</td>
<td>-1.42 [-3.40, 0.56]</td>
</tr>
<tr>
<td>Harris 2012</td>
<td>-0.55</td>
<td>3.61</td>
<td>43</td>
<td>-0.55</td>
<td>3.72</td>
<td>46</td>
<td>10.4%</td>
<td>0.00 [-1.52, 1.52]</td>
</tr>
<tr>
<td>Iraj 2012</td>
<td>1.09</td>
<td>3.17</td>
<td>20</td>
<td>2.19</td>
<td>3.39</td>
<td>20</td>
<td>7.2%</td>
<td>-1.10 [-3.13, 0.93]</td>
</tr>
<tr>
<td>Davidson 2013</td>
<td>-1.09</td>
<td>3.17</td>
<td>56</td>
<td>1.09</td>
<td>3.39</td>
<td>53</td>
<td>12.9%</td>
<td>-2.18 [-3.41, -0.95]</td>
</tr>
<tr>
<td>Dutta 2014</td>
<td>2.08</td>
<td>3.17</td>
<td>55</td>
<td>4.15</td>
<td>3.39</td>
<td>49</td>
<td>12.6%</td>
<td>-2.07 [-3.34, -0.80]</td>
</tr>
<tr>
<td>Solid 2014</td>
<td>1.31</td>
<td>3.17</td>
<td>242</td>
<td>1.42</td>
<td>3.61</td>
<td>242</td>
<td>19.7%</td>
<td>-0.11 [-0.72, 0.50]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>496</td>
<td></td>
<td></td>
<td>487</td>
<td>100.0%</td>
<td>-0.89</td>
<td>[1.54, -0.23]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.47; Chi² = 16.49, df = 8 (P = 0.04); I² = 51%

Test for overall effect: Z = 2.66 (P = 0.008)

The effect of vitamin D supplementation based on baseline 25(OH)D was inconclusive.
Main points-questions-T2DM???

- Does vitamin D deficiency predispose to DM?
- Does vitamin D substitution prevent DM?
- Does vitamin D substitution ameliorate glycemic control?
Several observational studies support vitamin D action.

However, there have been neutral studies.

Supplementation studies have failed to support the evidence (study design???)
Main points-questions-T2DM???

Does vitamin D deficiency predispose to DM?

Does vitamin D substitution prevent DM?

Does vitamin D substitution ameliorate glycemic control?
Vitamin D supplementation and glycemic control in type 2 diabetes patients: A systematic review and meta-analysis

Chunhua Wu, Shanhui Qiu, Xiangyun Zhu, Ling Li*
Department of Endocrinology, Zhengdu Hospital, Institute of Diabetes, Medical School, Southeast University, China

Vitamin D supplementation could be effective at improving glycemic control in vitamin D deficient or non-obese type 2 diabetes patients

A modest reduction of HbA1C after vitamin D treatment in adults with type 2 diabetes albeit with substantial heterogeneity between studies and no difference in FBG

The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies

Clare J. Lee a,b, Geetha Iyer b, Yang Liu b, Rita R. Kalyani a, N’Dama Bamba b,c,d, Colin B. Ligon e, Sanskriti Varma f, Nestoras Mathioudakis a

* Division of Endocrinology, Diabetes & Metabolism, The Johns Hopkins University, Baltimore, MD, USA
b The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
c Division of Infectious Diseases, The Johns Hopkins University, Baltimore, MD, USA
d Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD, USA
f Division of Immunology, The Johns Hopkins University, Baltimore, MD, USA
e The Johns Hopkins University School of Medicine, Baltimore, MD, USA
Fig. 1 - Flow chart of the multi-phase process for study selection.
Fig. 2 - Forest plots of meta-analysis of the effect of vitamin D supplementation on HbA1c. Data are pooled SMDs with 95% CIs. HbA1c: hemoglobin A1c; SMD: standardized mean difference, CI: confidence interval.
Fig. 3 - Forest plots of meta-analysis of the effect of vitamin D supplementation on FFG. Data are pooled SMDs with 95% CI. FFG: fasting blood glucose. SMD: standardized mean difference. CI: confidence interval.
What about type 1 DM???
Role of vitamin D in the pathogenesis of type 1 Diabetes Mellitus

Palomer et al, Diabetes, Obesity and Metabolism, 2008
Some evidence for north-south gradient

exceptions (e.g. Sardinia)

association diluted by variations in genetic susceptibility?

Little evidence for seasonal variation by time of birth in diabetic cases or according to season of the onset of the disease

multifactorial disease, latency may be long

confounded by use of vitamin D supplements, recommended during the dark seasons of the year
Vitamin D & Type 1 diabetes
- Studies in animals and humans

- Type 1 diabetes prevented by 1,25-(OH)_2D in animal models

- Some evidence for protective effect in humans

- only a few studies published to date
Vitamin D & Type 1 diabetes
- Relevant time window?

✨ Pregnancy

✨ mothers cod liver oil consumption ⇒ diabetes risk ↓

✨ Infancy

✨ any vitamin D supplementation ⇒ diabetes risk ↓

✨ dose of supplementation ↑ ⇒ diabetes risk ↓

✨ vitamin D deficiency ⇒ diabetes risk ↑

✨ Childhood ? Adolescence? Adulthood?
Intake of vitamin D and risk of type 1 diabetes: a birth cohort study

Elina Hyppönen, Esa Läärä, Antti Reunanen, Marjo-Riitta Järvelin, Suvi Virtanen

Lancet 2001;358:1500-1503
Northern Finland 1966 Cohort Study

- All pregnant mothers in the two northernmost provinces of Finland (Oulu and Lapland) with expected date of delivery in 1966 invited to participate - > 12,058 live births

- Information on vitamin D intake/status collected at 1 year of age (n=10, 366)

- Follow-up for type 1 diabetes up to December 1997

Hyppönen et al. Lancet 2001;358:1500-1503
**Incidence of type 1 diabetes by use of vitamin D supplements in infancy**

<table>
<thead>
<tr>
<th>Use of vitamin D supplements</th>
<th>Cases</th>
<th>Incidence /100,000 years at risk</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>2</td>
<td>204</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Irregularly</td>
<td>12</td>
<td>33</td>
<td>0.16 (0.04-0.72)</td>
<td>0.16 (0.04-0.74)</td>
</tr>
<tr>
<td>Regularly</td>
<td>67</td>
<td>24</td>
<td>0.12 (0.03-0.47)</td>
<td>0.12 (0.03-0.51)</td>
</tr>
</tbody>
</table>

* Adjusted for neonatal, social and anthropometric factors.

Hyppönen et al. Lancet 2001;358:1500-1503
## Incidence of type 1 diabetes by dose of vitamin D supplementation

<table>
<thead>
<tr>
<th>Dose of Vitamin D†</th>
<th>Cases</th>
<th>Incidence /100,000 years at risk</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2</td>
<td>96</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Recommended</td>
<td>63</td>
<td>24</td>
<td>0.20 (0.05-0.84)</td>
<td>0.21 (0.05-0.88)</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td>15</td>
<td>0.14 (0.02-0.97)</td>
<td>0.14 (0.02-1.01)</td>
</tr>
</tbody>
</table>

* Adjusted for neonatal, social and anthropometric factors.
† Dose has been presented for infants receiving vitamin D regularly.

Hyppönen et al. Lancet 2001;358:1500-1503
Incidence of type 1 diabetes by suspected rickets in infancy

<table>
<thead>
<tr>
<th>Suspected rickets</th>
<th>Cases /100,000 years at risk</th>
<th>Incidence</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>77</td>
<td>25</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>62</td>
<td>2.6 (1.0-7.2)</td>
<td>3.0 (1.0-9.0)</td>
</tr>
</tbody>
</table>

* Adjusted for neonatal, social and anthropometric factors.
Associated temporal changes?
(in Finland)

- Increasing incidence of type 1 diabetes
- Dose reduction in infant vitamin D recommendations
  - 1956: 4000-5000 IU
  - 1964: -> 2000 IU
  - 1975: -> 1000 IU
  - 1992: -> 400 IU
- Changes in the compliance of giving vitamin D?
- Increase in the incidence of rickets during 1980s
Protective effects of $1\alpha$-hydroxyvitamin D3 on residual $\beta$-cell function in patients with adult-onset latent autoimmune diabetes (LADA)

Figure 1. Changes of fasting and postprandial C-peptide levels during the treatment period. Data are shown as median. (A) Changes of fasting C-peptide; (B) Changes of postprandial C-peptide levels. * When compared with baseline, $P < 0.05$. Fasting C-peptide levels in insulin alone group decreased from 368 pmol/L at entry to 208 pmol/L at 6th month ($P = 0.02$), and to 179 pmol/L at 12th month ($P = 0.006$). No significant changes were found in the group treated with insulin plus vitamin D.
Combined treatment with sitagliptin and vitamin D in a patient with latent autoimmune diabetes in adults

E Rapti¹, S Karras¹, M Grammatiki¹, A Mousiolis¹, X Tsekmekidou¹, E Potolidis¹, P Zebekakis¹, M Daniilidis² and K Kotsa¹

¹Diabetes Center of 1st Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece and ²1st Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece

Correspondence should be addressed to K Kotsa
Email kalmanthou@yahoo.gr
Most studies support vitamin D action

However there have been neutral studies

Again there is need for carefully designed interventional studies!!!!!
The BIG public health question

IF the association between vitamin D and type 1 diabetes is shown to be causal, is it because...

...the intake is too low only to prevent the destructive autoimmune reaction in susceptible individuals?

OR

...the intake is too low to prevent human immune system from developing/working optimally?
Uncertainties.....

- **Study design**
- Relation between 25(OH)D--1,25 (OH)2D ----- PTH -------????
- Relation between 25(OH)D and other confounders (BMI, exercise)
- Genetic factors (SNPs DBP)
- Tissue 1,25(OH)2D production as opposed to blood concentrations!!
RESEARCH ARTICLE

1,25-Dihydroxyvitamin D to PTH(1–84) Ratios Strongly Predict Cardiovascular Death in Heart Failure

Damien Gruson¹,² *, Benjamin Ferracin¹, Sylvie A. Ahn³, Claudia Zierold⁴, Frank Blocki⁴, Douglas M. Hawkins⁵, Fabrizio Bonelli⁴, Michel F. Rousseau³

¹ Pôle de recherche en Endocrinologie, Diabète et Nutrition, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium, ² Department of Laboratory Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium, ³ Division of Cardiology, Cliniques Universitaires St-Luc and Pôle de recherche cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium, ⁴ DiaSorin Inc, 1951 Northwestern Avenue, Stillwater, Minnesota, 55082, United States of America, ⁵ School of Statistics, University of Minnesota, Minneapolis, Minnesota, 55455, United States of America
The combined effect of vitamin D and parathyroid hormone concentrations on glucose homeostasis in older patients with prediabetes: a cross-sectional study

Spyridon N. Karras 1, Panagiotis Anagnostis 2, Vasiliki Antonopoulou 1, Xanthipi Tsekmekidou 1, Theocharis Koufakis 1, Dimitrios G. Goulis 2, Pantelis Zebekakis 1, Kalliopi Kotsa 1

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The aim of this study was to examine the role of PTH / Vit_D axis on glucose homeostasis in elderly persons with prediabetes (preDM).

Subjects / Methods: Patients with preDM (n = 144) and healthy age-matched controls (n = 81) with normal fasting glucose were included in this cross-sectional study. Study parameters included anthropometric characteristics, morning fasting glucose (FPG), insulin (FPI), PTH, 25-hydroxyvitamin D [25(OH)D], Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Homeostasis Model Assessment of β-cell function (HOMA-β). Both groups were stratified into subgroups according to Vit_D status and tertiles of PTH.

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Vit D deficiency was prevalent in both groups. Eighty-two participants (57%) in the preDM group, and 56 in NFG group (69%) were 25(OH)D deficient (p = 0.451). Participants, with vit D deficiency, did not differ according to FPG and FPI as well as HOMA-IR and HOMA-β, compared with those who were vit D sufficient, for both PreDM and NFG groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>25(OH)D status</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Deficient *</td>
<td>Sufficient *</td>
</tr>
<tr>
<td>FPI (µU/mL)</td>
<td>NFG</td>
<td>9.8 ± 0.7</td>
<td>8.4 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>10.9 ± 0.6</td>
<td>11.5 ± 0.8</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>NFG</td>
<td>2.26 ± 0.19</td>
<td>2.16 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>2.81 ± 0.18</td>
<td>2.90 ± 0.21</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>NFG</td>
<td>93.5 (91.5 - 95.5)</td>
<td>93.8 (91.8 - 95.8)</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>100.7 (98.7 - 102.7)</td>
<td>101.4 (99.4 - 103.4)</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>NFG</td>
<td>96.38 (94.20 - 98.57)</td>
<td>91.00 (88.7 - 93.27)</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>93.97 (91.84 - 96.11)</td>
<td>98.63 (96.46 - 100.79)</td>
</tr>
</tbody>
</table>

* Vitamin D status is defined by 25(OH)D levels. Vitamin D deficient is defined as 25(OH)D < 20ng/ml and sufficient as 25(OH)D > 20ng/ml.

Abbreviations: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β-cell function; FPI: Fasting Plasma Insulin; FPG: Fasting Plasma Glucose; NFG: Normal Fasting Glucose; PreDM: Prediabetes Mellitus; 25(OH)D: 25-hydroxyvitamin D.
PTH subgroups did not differ in relation to HOMA-IR, HOMA-β and insulin, concentrations, after accounting for the demographic covariates for NFG group. However, in the PreDM group, FPG differed significantly across PTH tertiles, increasing from the 1\textsuperscript{st} to 2\textsuperscript{nd} to 3\textsuperscript{rd} tertile ($p = 0.011$, across all groups), after adjusting for age, gender, BMI and season of sampling. No differences in parameters of glycemic homeostasis were observed among other subgroups of PTH tertiles.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>$\leq 20-40$ (A)</th>
<th>20-40 (B)</th>
<th>$\geq 40$ (C)</th>
<th>$p$-value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPI</td>
<td>NFG</td>
<td>9.9 ± 0.9</td>
<td>9.4 ± 1.2</td>
<td>8.8 ± 1.0</td>
<td>0.747</td>
</tr>
<tr>
<td>(µU/mL)</td>
<td>PreDM</td>
<td>9.3 ± 0.9</td>
<td>12.1 ± 0.8</td>
<td>11.6 ± 0.9</td>
<td>0.051</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>NFG</td>
<td>2.26 ± 0.24</td>
<td>2.31 ± 0.32</td>
<td>2.12 ± 0.28</td>
<td>0.900</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>2.37 ± 0.24</td>
<td>3.06 ± 0.21</td>
<td>3.06 ± 0.24</td>
<td>0.065</td>
</tr>
<tr>
<td>FPG</td>
<td>NFG</td>
<td>92.9</td>
<td>93.8</td>
<td>94.2</td>
<td>0.885</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>PreDM</td>
<td>(90.9 - 94.9)</td>
<td>(91.8 - 95.8)</td>
<td>(92.2 - 96.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>NFG</td>
<td>96.61</td>
<td>93.54</td>
<td>92.47</td>
<td>0.978</td>
</tr>
<tr>
<td></td>
<td>PreDM</td>
<td>(94.35 - 98.86)</td>
<td>(91.19 - 95.89)</td>
<td>(90.17 - 94.77)</td>
<td>0.650</td>
</tr>
</tbody>
</table>

$^a$p-value refers to comparisons across all groups; $^b$A vs B $p=0.013$, A vs C $p=0.006$, B vs C $p=0.039$. 

*Table 3: Impact of PTH status on glycemic status (FPG), insulin resistance (Fasting Insulin and HOMA-IR) and insulin secretion (HOMA-β) for PreDM and NFG diagnosis group separately.*
There was an increasing trend for both FPI and FPG according to PTH tertiles, which resulted in significantly higher concentrations in participants classified as vit D deficiency / PTH 3rd tertile compared to all other groups (p = 0.031 and 0.027, respectively). Participants with vit D sufficiency / PTH 3rd tertile demonstrated increased FPI concentrations (p = 0.015), compared with those with vit D sufficiency / PTH 1st - 2nd tertile, after adjustment for age, gender, BMI and season of sampling. Participants with vit D sufficiency / PTH 3rd tertile had increased FPG compared with those with vit D sufficiency / PTH 1st - 2nd tertile (p = 0.024) and those with vit D deficiency / PTH 1st - 2nd tertile (p = 0.018). HOMA-IR was significantly higher in PreDM group in the vit D deficiency / PTH 3rd tertile (p = 0.039) compared to all other groups. These results were also evident (p = 0.038) for participants with vit D sufficiency / PTH 3rd tertile, compared with participants with vit D sufficiency / PTH 1st - 2nd tertile. No statistical differences for HOMA-β were observed among groups.
NEW EMERGING CALCIOTROPIC HORMONES NORMS FOR METABOLIC COMPLICATIONS???

Or in other words........

the Vitamin D metabolic system needs its ......”TSH” in analogy with the thyroid hormone system to accurately and finely tune and estimate levels and therapeutic results!!!!!!!
Serum 25(OH)D measured in elderly people in 16 European centers participating in the Euronut SENECA Study.

The lowest values were found in Greece, Spain, and Italy.
Associations of vitamin D status with dietary intakes and physical activity levels among adults from seven European countries: the Food4Me study

Yannis Manios¹,¹⁴ · George Moschonis¹ · Christina P. Lambrinou¹ · Christina Mavrogianni¹ · Lydia Tsirigoti¹ · Ulrich Hoeller² · Franz F. Roos² · Igor Bendik² · Manfred Eggersdorfer² · Carlos Celis-Morales³ · Katherine M. Livingstone³ · Cyril F. M. Marsaux⁴ · Anna L. Macready⁵ · Rosalind Fallaize⁵ · Clare B. O’Donovan⁶ · Clara Woolhead⁶ · Hannah Forster⁶ · Marianne C. Walsh⁶ · Santiago Navas-Carretero⁷ · Rodrigo San-Cristobal⁷ · Silvia Kolossa⁸ · Jacqueline Hallmann⁸ · Mirosław Jarosz⁹ · Agnieszka Surwiło⁹ · Iwona Traczyk⁹ · Christian A. Drevon¹⁰ · Ben van Ommen¹¹ · Keith Grimaldi¹² · John N. S. Matthews¹³ · Hannelore Daniel⁸ · J. Alfredo Martinez⁷ · Julie A. Lovegrove⁵ · Eileen R. Gibney⁶ · Lorraine Brennan⁶ · Wim H. M. Saris⁴ · Mike Gibney⁶ · John C. Mathers³ · on behalf of the Food4Me Study

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Fig. 1 Prevalence of vitamin D insufficiency and deficiency by country. †P<0.05 for the differences in the prevalence of vitamin D deficiency (25-OHD$_3$ < 30 nmol/L) between countries sharing the same symbol.
Research Article

Thyroid Autoimmunity in the Context of Type 2 Diabetes Mellitus: Implications for Vitamin D

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<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Type 2 diabetes mellitus</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>234</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>Male gender (female)</td>
<td>89 (38)</td>
<td>109 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.2 (6.5)</td>
<td>67.6 (9.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.6 (4.9)</td>
<td>31.6 (5.7)</td>
<td>0.032</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus duration (years)</td>
<td>N/A</td>
<td>10.0 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Glycated haemoglobin (%)</td>
<td>4.7 (0.5)</td>
<td>7.1 (1.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>25-Hydroxy-vitamin D (ng/mL)</td>
<td>22.6 (12.6)</td>
<td>16.5 (10.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presence of vitamin D deficiency/insufficiency</td>
<td>172 (73.5%)</td>
<td>215 (81.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Thyroid peroxidase Ab (IU/mL)</td>
<td>60 (156)</td>
<td>90 (200)</td>
<td>0.005</td>
</tr>
<tr>
<td>Thyroglobulin Ab (IU/mL)</td>
<td>44 (131)</td>
<td>54 (136)</td>
<td>NS</td>
</tr>
<tr>
<td>Thyroid autoimmunity</td>
<td>18 (7.7)</td>
<td>38 (14.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (µIU/mL)</td>
<td>1.95 (1.60)</td>
<td>2.25 (3.64)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8 (3.4)</td>
<td>11 (4.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented as mean (standard deviation) or N (%). P values refer to Mann-Whitney test or Pearson chi-square. NS: nonsignificant at the level of 0.05. Abs: autoantibodies.
So how do we select diabetic patients to measure vitD??

- We don’t, we test them all!!!
- We do not test, we just supplement everybody!!!
- We establish risk scores and high risk groups!
What are the optimal 25-(OH)-D levels?

Defficiency: <10 ng/mL
Insufficiency: ≥10 and <20 ng/mL
Partial Insufficiency: ≥20 to <30 ng/mL

Recommendation:
The target level should be greater than 50 nmol/L at the end of winter. Each laboratory should be encouraged to report the same decision limits.

Most adults will eventually need vitamin D supplements due to insufficient sun exposure and dietary habits that do not support 25-(OH)-D level ≥30 ng/mL all year through

800 IU/day vitD₃ seems to be adequate to support ADEQUATE levels

Adequate levels are???
Vitamin D actions in pancreatic and immune cells suggest a possible protective role in T2DM prevention and treatment. Data have been inconsistent due mainly to study design. More consistent data for T1DM have made supplementation necessary for treatment and prevention of the disease. There are problems with existing measurement methods and optimal cut-off values and therefore universal substitution cannot be advised (for now).

Risk assessment scores should be developed. Combining vitamin D values with other parameters (i.e. PTH) may help in the future.