Vitamin D – beyond the bone

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HISTORY OF VITAMIN D ...

- **17-th century**
  - Whistler & Glisson – rickets described

- **20-th century**
  - Mellanby - experimental rickets in dogs
  - McCollum – a new fat soluble substance from fish oil
  - Hess & Goldblatt - UV light and vitamin D biosynthesis
  - Windaus - vitamin D chemical structure
  - Bessau - vitamin D in rickets prophylactics
  - De Luca & Blunt - vitamin D metabolism
  - Gets - vitamin D as a hormone
  - vitamin D receptor (VDR)

- **Nowadays** - vitamin D non-calcemic role
VITAMIN D IN NATURE

Cholecalciferol (Vitamin D3)

Ergocalciferol (Vitamin D2)
Biosynthesis and Metabolism

Skin

7-dehydrocholesterol

Vitamin D₃

CYP27A1
CYP2R1
CYP2J2/3
CYP3A4
CYP2D25
CYP2C11

25-hydroxylase

Diet

Fish

Liver

1α,25(OH)₂D₃

1α-hydroxylase

25(OH)D₃
**1A-HYDROXYLASE: REGULATOR OF CALCITRIOL SYNTHESIS**

**Extrarenal 1α-hydroxylase**
- Paracrine and autocrine pathway
- 25(OH)D₃
- Extrarenal CYP27B1
- EGF
- Local synthesis
- CYP24A1
- 1,25(OH)₂D₃
- Anticancer actions
- Degradation
- 1,24,25(OH)₃D₃

**Renal 1α-hydroxylase**
- Endocrine pathway
- 25(OH)D₃
- Renal CYP27B1
- Mineral homeostasis
- PTH
- FGF23
- Low Ca²⁺
- Renal synthesis
- CYP24A1
- 1,25(OH)₂D₃
- Degradation
- 1,24,25(OH)₃D₃

*Nature Reviews Cancer 14, 342–357 (2014)*
Slow effects – ~ 3000 genes
- Bone metabolism
- Mineral homeostasis
- Intestinal Ca\(^{2+}\) transport
- Renal phosphate reabsorption
- Xenobiotic detoxification
- Cell cycle control
- Cell life in mammalian hair cycle
- Immune antimicrobial peptides
- Homocysteine metabolism

Rapid effects
- Opening voltage-gated Cl/Ca-channels
- Second messengers generation
- Rapid stimulation of Ca absorption
- Insulin secretion from pancreatic β-cells
- Exocytosis
CALCITRIOL: CLASSICAL EFFECTS

• Classical (endocrine pathway)
  – regulation of Ca and phosphate plasma levels by its effect on gut, bones and parathyroid glands
Non-classical (paracrine and authocrine pathway)
- Cell differentiation
- Anticancer
- Antiproliferative
- Antibacterial
- Anti-inflammatory
- Immunomodulatory
- Antihypertensive...
1. Antiproliferative and antineoplastic activity

inhibits signaling pathways related to specific cancer growth
2. Immunomodulatory activity

CALCITRIOL AND NON-SKELETAL HEALTH

Inhibits NF-κB and P38MAPK signaling and gene transcription of pro-inflammatory factors.

Inhibits pro-inflammatory cytokines and chemokines secretion.
• **Vitamin D deficiency:**
  25(OH)D \(< 25\) nmol/L (10 ng/mL)

• **Vitamin D insufficiency:**
  25(OH)D \(25 \sim 50\) nmol/L (10-20 ng/mL) – severe
  \(50 \sim 75\) nmol/L (20-30 ng/mL) – low

• **Vitamin D sufficiency:**
  25(OH)D = \(75 \sim 100\) nmol/L (30-40 ng/mL)
Bulgaria: 75.8% of the Bulgarian population (20–80 years) - 25OHD <50 nmol/L, of them 21.3% - deficient (<25 nmol/L); 54.5% - insufficient (25–50 nmol/L). (A.-M. Borissova et al. Nutrition and Aging 3 (2015) 107–113)
VITAMIN D DEFICIENCY

**CAUSES**
- Synthesis:
  - Melanin
  - Sunscreens
  - Latitude
  - Winter season
- Drugs:
  - Antiepileptic
  - Glucocorticoids
  - Tuberculostatics
  - HAART
- Malabsorption:
  - Crohn’s
  - Whipple’s
  - Cystic fibrosis
  - Celiac disease
  - Cholestasis

**CONSEQUENCES**
- CNS:
  - Schizophrenia
  - Depression
- CVS:
  - Hypertonia
- Infectious diseases:
  - TBC
  - Flu
- Metabolic syndrome:
  - Skeletal muscles: Weakness, pain
- Bones:
  - Osteoarthritis
  - Osteoporosis/osteomalacia
  - Rickets
- Cancer:
  - Breast
  - Colon
  - Pancreas
  - Prostate

**Drugs**
- Liver diseases
- Renal failure
- Obesity
ORIGINAL ARTICLE

Serum 25-Hydroxy Vitamin D Levels in Bulgarian Patients with Prostate Cancer: a Pilot Study

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SUMMARY

Background: The antiproliferative effect of the active form of vitamin D on cancer cells and its ability to induce cell differentiation and suppression of tumor-induced angiogenesis in the last decade has provoked enormous research for the elucidation of its role in the prevention of different types of cancer and in slowing down the malignancy progression. The aim of the present pilot study was to determine the circulating 25-hydroxy vitamin D (25OHD) levels in Bulgarian prostate cancer (PCa) patients and to investigate their relationship with various determinants associated with the severity and progression of the disease.
Aim: to determine the circulating 25OHD levels in Bulgarian prostate cancer (PCa) patients and to investigate their relationship with various determinants, associated with the severity and progression of the disease.

Patients: 53 PCa and 30 patients with benign prostate hyperplasia (BPH); systemic transrectal ultrasound-guided tru-cut prostate biopsy

Methods: 25OHD, PSA, tumor grade (Gleason grading system)

Vitamin D and prostate cancer – our experience

• Vitamin D insufficiency in 80% of the tested PCa and in 64% of BPH patients, regardless the season;
• Moderate negative correlation between vitamin D status and clinical laboratory determinants of PCa, such as PSA and Gleason score.
Prevalence of vitamin D deficiency and insufficiency in Bulgarian patients with chronic Hepatitis C viral infection

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Abstract

Aims. The present pilot study aimed to determine vitamin D status in Bulgarian patients with chronic HCV infection in respect to the severity of liver disease and response to interferon-ribavirin therapy. Methods. The study encompassed 296 patients: 161 males (54.4%) aged 42.08 ± 14.87 years, 135 females (45.6%) aged 45.72 ± 14.34 years, 86.5% of them infected with HCV genotype 1. Total 25-hydroxyvitamin-D (25OHD) was determined by liquid chromatography/
Aim. To determine vitamin D status in Bulgarian patients with chronic HCV infection in respect to the severity of liver disease and response to interferon-ribavirin therapy.

Patients: 296 patients: 161 males, 135 females.

Methods: 25OHD, HCV genotype, HCV RNA viral load, liver function tests, Histology: liver biopsy for fibrosis stage and grade (METAVIR system), Antiviral therapy: PEG-IFN plus ribavirin, viral response after therapy monitored.

- More than 80% of HCV-infected patients were vitamin D deficient and insufficient;
- Inverse relationship between 25OHD levels and viral load, liver fibrosis and treatment outcomes.
Vitamin D status in children with acute diarrhea

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Abstract

Vitamin D deficiency is highly prevalent among children worldwide. It includes impaired immune response to infection and decreased activity of gut antimicrobial peptides. Elucidating the impact of vitamin D deficiency for the severity of acute diarrhea among children may be helpful for the disease management. Determination of vitamin D status in toddlers with acute diarrhea and evaluation the relationship with diarrhea severity. 77 children (1.0–3.5 years) with acute diarrhea, hospitalized in the Department of Infectious diseases were enrolled in the study. The patients were divided into 2 groups: with risk factors for severe diarrhea (group A, n=30) and group B without risk factors (n=47). The severity of diarrhea was assessed by the number of stools. The levels of circulating vitamin D were assayed by liquid chromatography with tandem mass-spectrometric detection. One way ANOVA and Kruskal Wallis statistics were used for statistical analysis. Patients in group A were vitamin D insufficient (median 53.63 nmol/L), compared to group B (median 66.09 nmol/L), p<0.05. Vitamin D deficiency (median 49.20 nmol/L) was detected in children with severe diarrhea (>20 stools) vs vitamin D in children (median 64.83 nmol/L) with less intensive diarrhea, p<0.05. An inverse relationship was observed between the severity of diarrhea and serum 25(OH)D levels.
Patients:
• 77 children with acute diarrhea
  • Age 1 - 3.5 years
• 2 study groups: A - with risk factors for diarrhea; B - without risk factors

Results:
• 63.6% of the studied patients: suboptimal vitamin D status, 25OHD < 75 nmol/L
• 9 patients: severe deficiency, 25OHD < 25 nmol/L;
• 16 patients: mild deficiency, 25OHD between 25 and 50 nmol/L;
• 24 patients: insufficiency, 25OHD in the range 50-75 nmol/L.

CALCITRIOL AND NON-SKELETAL HEALTH
Vitamin D status and acute diarrhea in toddlers – our experience

Figure 1. Mean 25OHD3 levels in patients with (group A) and without risk factors for severe diarrhea (group B).

Figure 3. Mean serum 25OH vitD3 in patients with different diarrhea intensity.
Association between vitamin D status and obesity in Bulgarian pre-pubertal children: a pilot study

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ABSTRACT

Background: It is considered that obesity and metabolic syndrome are accompanied with vitamin D deficiency. We aimed to examine the interrelations between vitamin D status and biomarkers for metabolic syndrome in Bulgarian pre-pubertal children.

Methods: The study enrolled 51 pre-pubertal children (29 boys, 22 girls) examined for serum 25-hydroxyvitamin D, and routine parameters for metabolic syndrome. Obesity was evaluated by body mass index and waist circumference.

Results: More than half (57.1%) of the studied children were vitamin D deficient, prevalent in girls than in boys (65.0% vs. 51.7% respectively). A tendency for worse metabolic status in the vitamin D-deficient group, expressed by higher fasting insulin, total cholesterol, total cholesterol/HDL-ratio and Homeostasis Model Assessment (HOMA)-index was observed. A trend for negative correlation was established between 25-hydroxyvitamin D and waist circumference, HOMA-index, and fasting insulin.

Conclusions: Vitamin D deficiency and inverse relationships between 25-hydroxyvitamin D and waist circumference, HOMA-index, and insulin were found amongst studied children.

Keywords: 25-hydroxyvitamin D, Pre-pubertal children, Obesity, Insulin resistance
• 57.1% of tested children were vitamin D deficient, more prevalent in girls than in boys (65.0% vs. 51.7%);

• **Worse metabolic status** in the vitamin D deficient group - higher fasting insulin, total cholesterol, total cholesterol/HDL ratio and HOMA-index;

• **Negative associations** between 25OHD and WC, HOMA-index, iPTH, and fasting insulin.
SUMMARY

• Vitamin D **insufficiency/deficiency** in risk groups of patients PCa, Hepatitis C viral infection, acute diarrhea, overweight/obesity;
• **Moderate linear correlation** with clinical determinants and biochemical parameters related to disease;
• **Improvement** of vitamin D status may have beneficial effect for prevention and course of disease of these risk groups of patients.
Vitamin D Deficiency Contributed to Mozart’s Death?

- Mostly composed at night;
- Latitude of Vienna, 48º N - impossible to make vitamin D from solar UVB for 6 months of the year;
- Died on December 5, 1791 - into the vitamin D winter;
- 1762 - 1783, October - May suffered many infectious diseases;
- 4 to 6 weeks half-life of 25OHD - his serum 25OHD levels would have been very low;
- Low serum 25OHD - risk factor for many of the diseases, causing death for that period in Vienna.

Research team

- Department of Biochemistry
  - Molecular medicine and Nutrigenomics
- Department of General medicine and Clinical Laboratory
- University Hospital “St. Marina”
  - Clinic of Urology
  - Clinic of Internal Diseases
  - Clinic of Pediatrics
  - Clinic of Infectious diseases

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I can no other answer make but thanks, and thanks; and ever thanks.

- William Shakespeare
  (Twelfth Night, Act 3, Scene 3)