NuGO week 2017

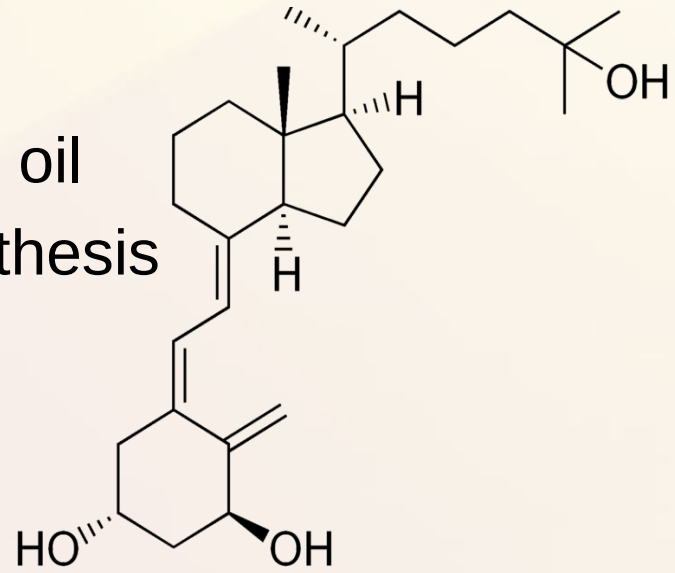
Vitamin D – beyond the bone

B. Galunska

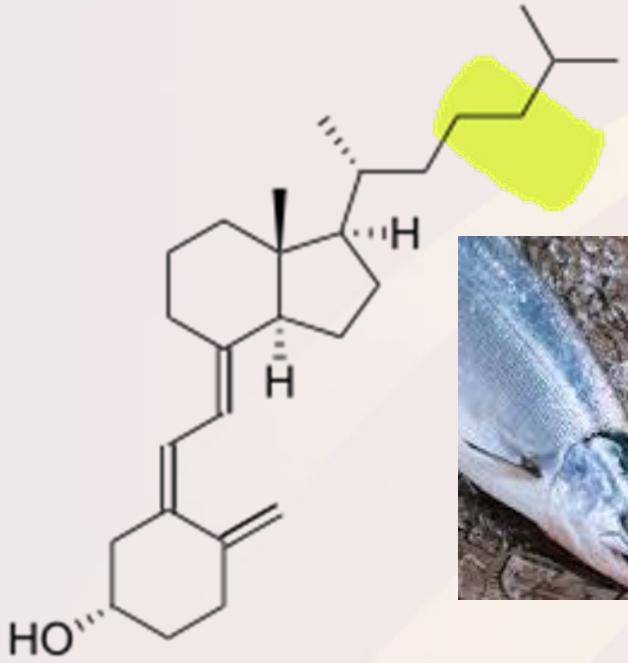
Department of Biochemistry,
Molecular medicine and Nutrigenomics
Pharmacy faculty, Medical University – Varna, Bulgaria

HISTORY OF VITAMIN D …

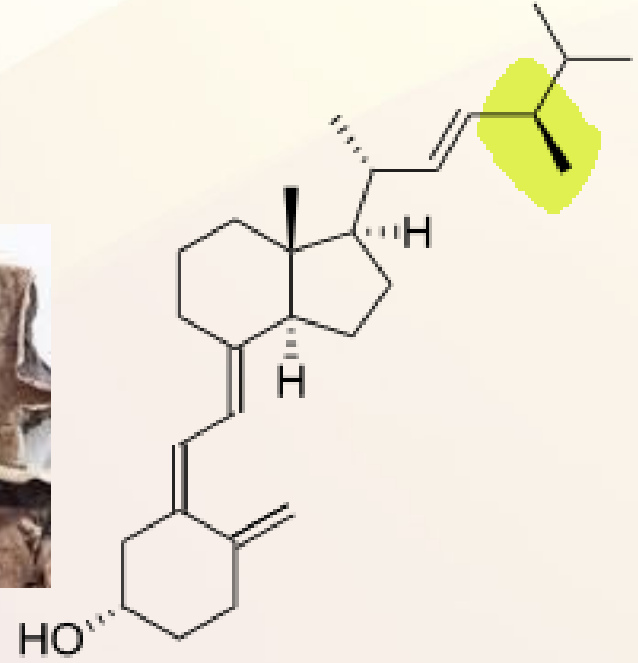
- **17-th century**
  - ✓ **Whistler & Glisson** – rickets described
- **20-th century**
  - ✓ **Mellanby** - experimental rickets in dogs
  - ✓ **McCollum** – a new fat soluble substance from fish oil
  - ✓ **Hess & Goldblatt** - UV light and vitamin D biosynthesis
  - ✓ **Windaus** - vitamin D chemical 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

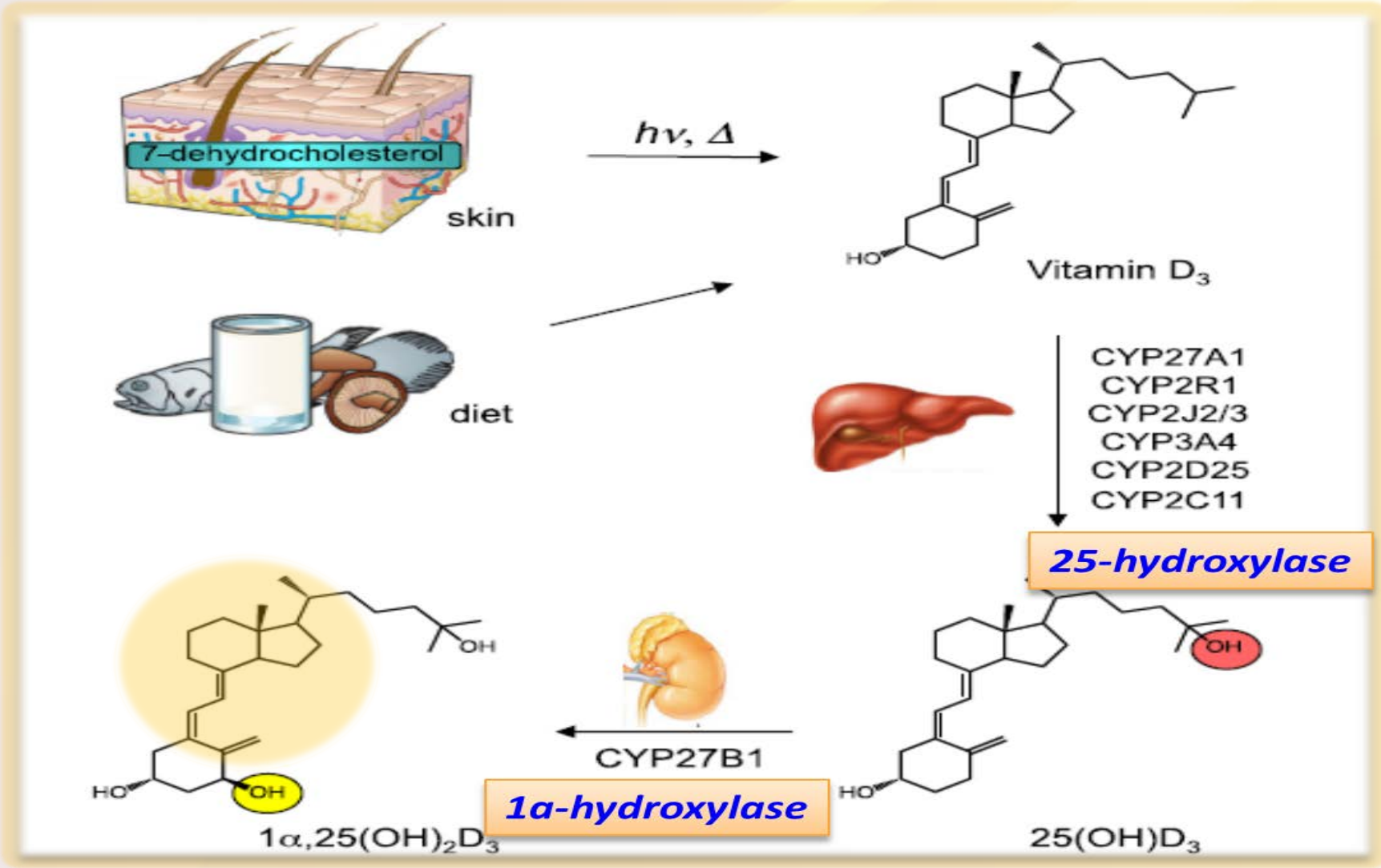


Cholecalciferol
(Vitamin D3)



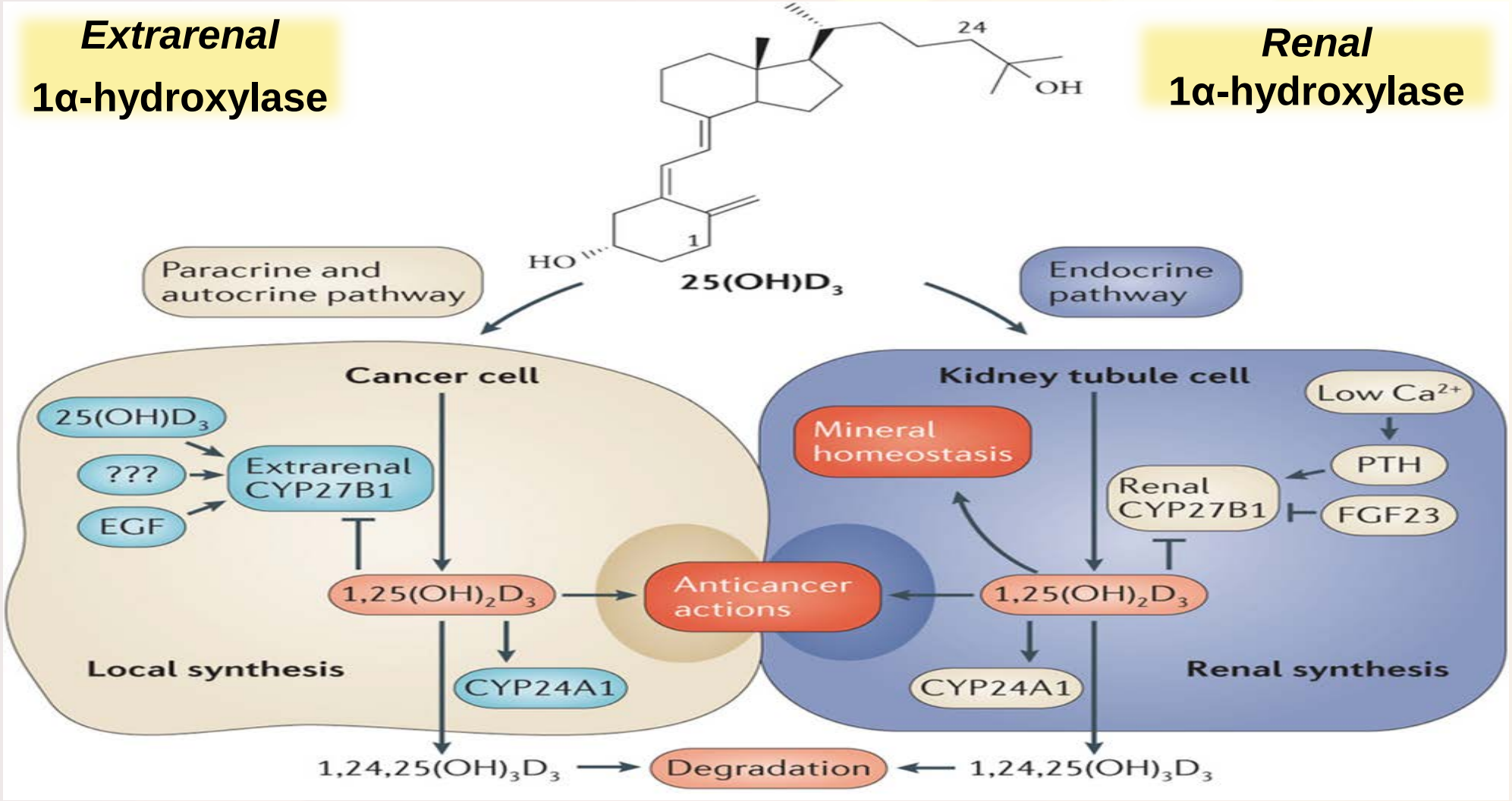
Ergocalciferol
(Vitamin D2)

BIOSYNTHESIS AND METABOLISM

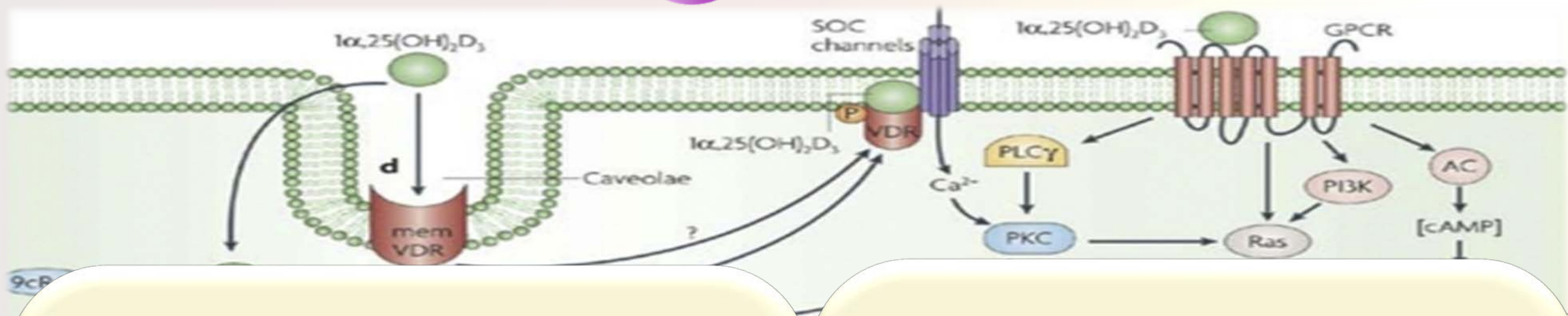


Johnes. Scandinavian Journal of Clinical & Laboratory Investigation, 2012; 72(Suppl 243): 7–13

1A-HYDROXYLASE: REGULATOR OF CALCITRIOL SYNTHESIS



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

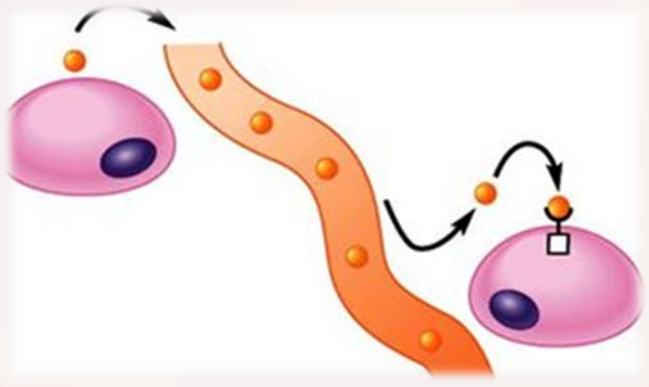
Rapid effects

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

M.R. Haussler et al. Best Practice & Res Clin Endocrinol & Metab 25 (2011) 543–559

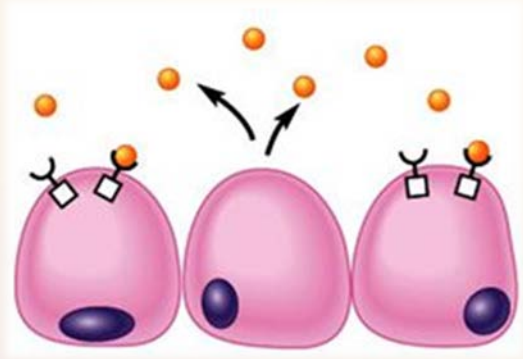
CALCITRIOL: CLASSICAL EFFECTS

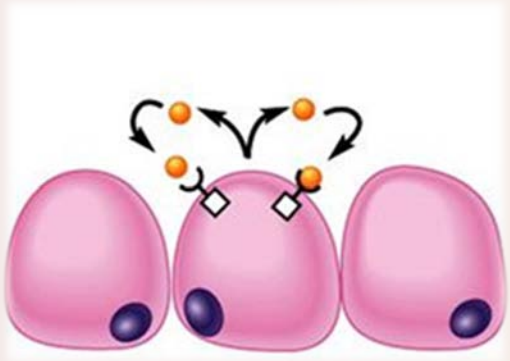
- **Classical (endocrine pathway)**
  - regulation of Ca and phosphate plasma levels by its effect on gut, bones and parathyroid glands



CALCITRIOL: NON-CLASSICAL EFFECTS

- **Non-classical (paracrine and authocrine pathway)**
  - Cell differentiation
  - Anticancer
  - Antiproliferative
  - Antibacterial
  - Anti-inflammatory
  - Immunomodulatory
  - Antihypertensive…



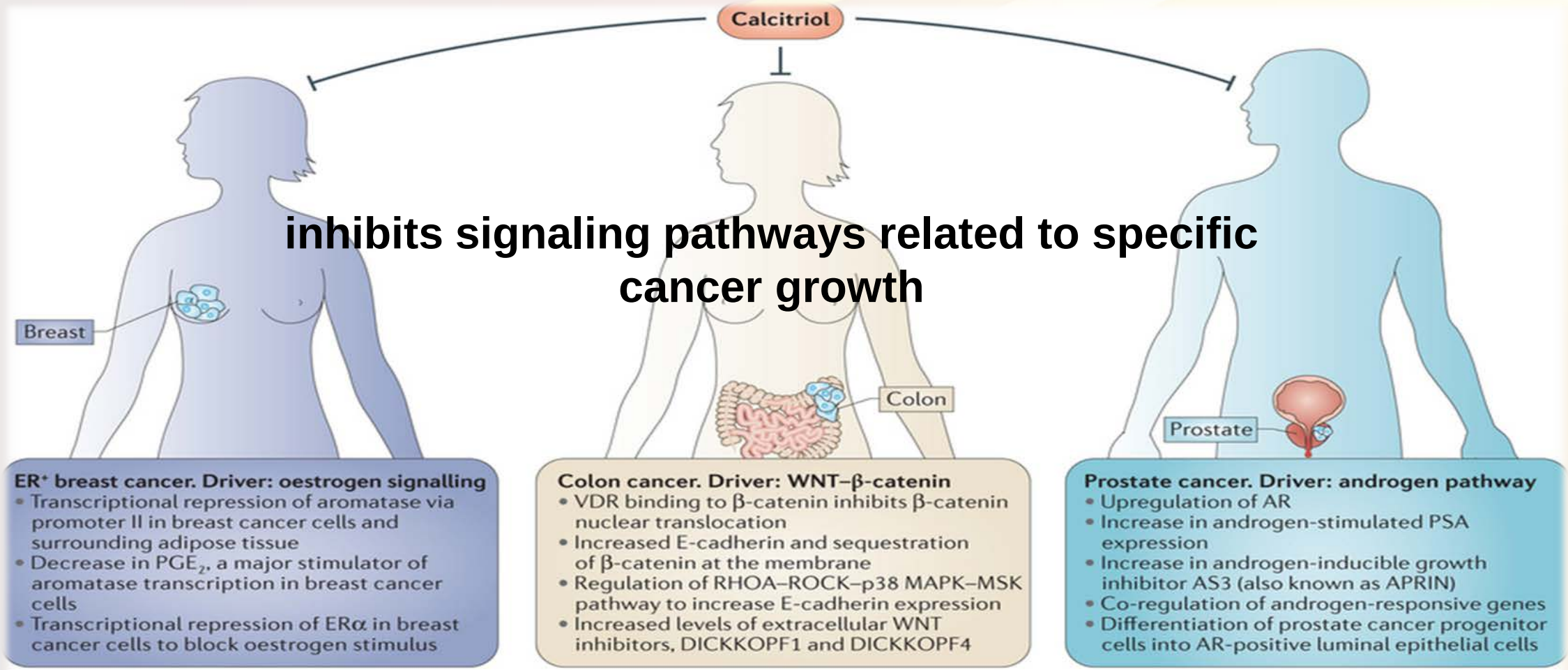


Lerchbaum and Obermayer-Pietsch. Eur J Endocrinol, 2012; 166: 765-778

CALCITRIOL AND NON-SKELETAL HEALTH

1. *Antiproliferative and antineoplastic* activity

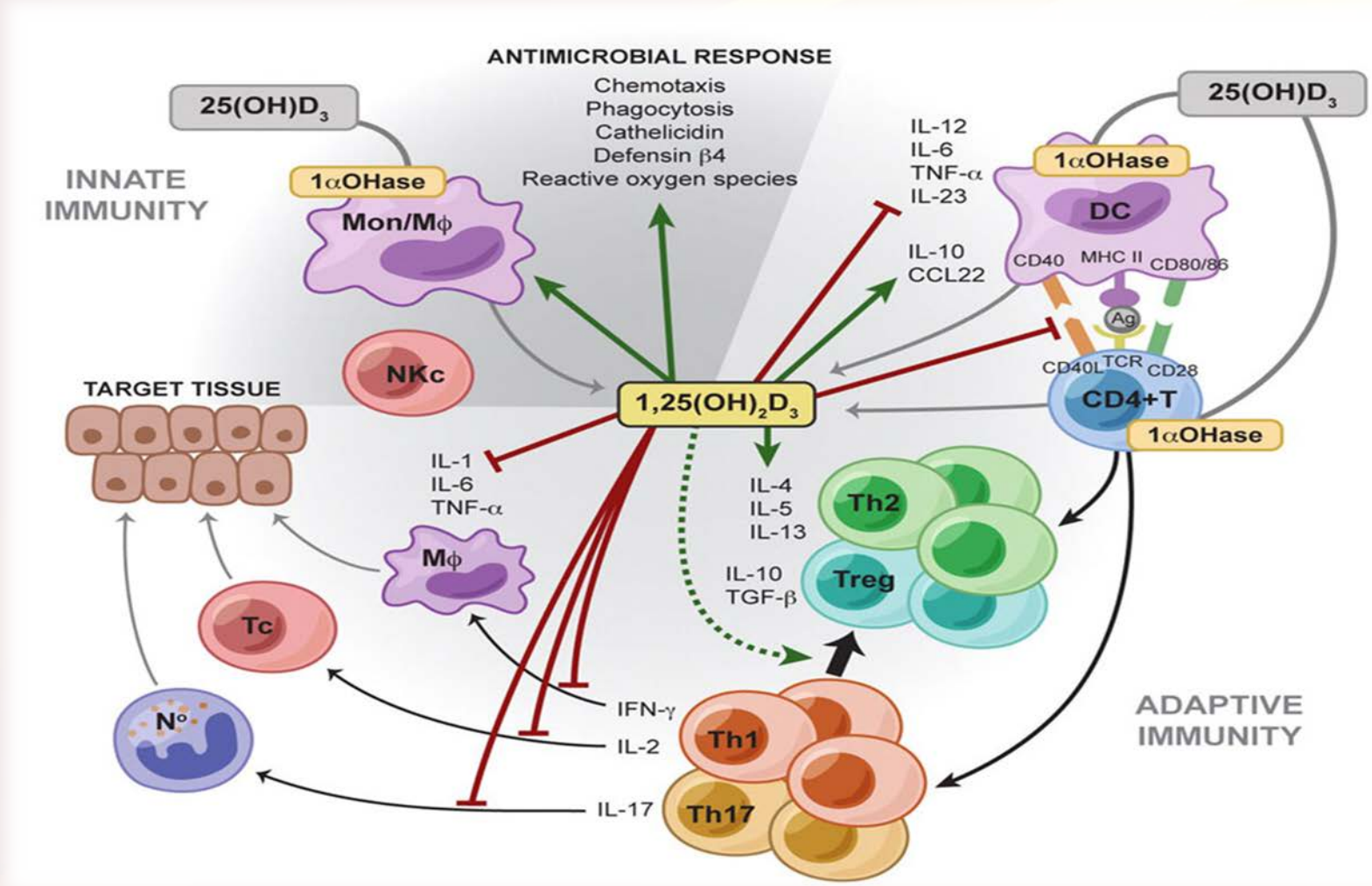
inhibits signaling pathways related to specific cancer growth



Nature Reviews | Cancer

CALCITRIOL AND NON-SKELETAL HEALTH

2. Immunomodulatory activity



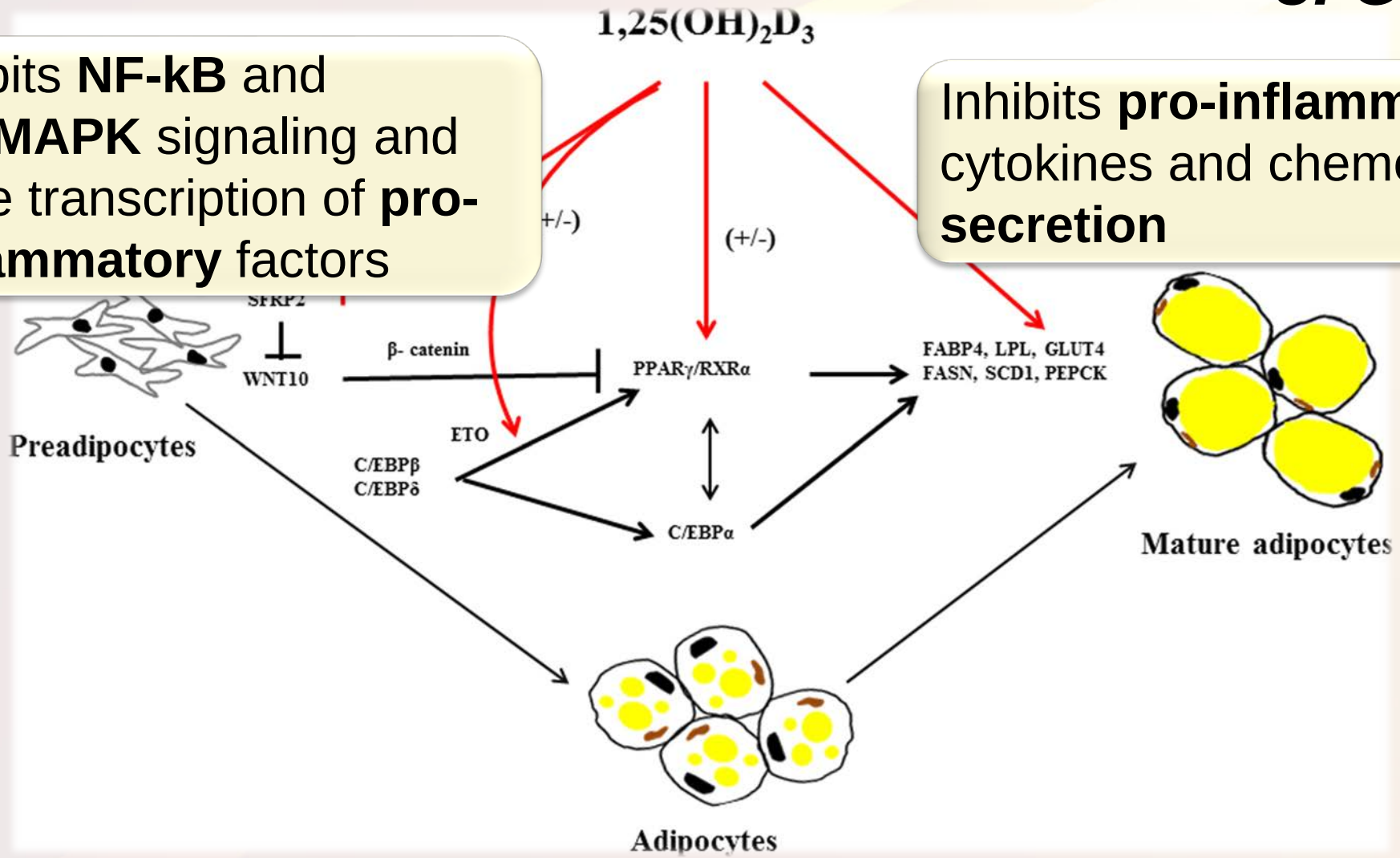
Iruretagoyena M, et al (2015) Front. Immunol. 6:513; Prietl et al. Nutrients 2013, 5:2502-2521

CALCITRIOL AND NON-SKELETAL HEALTH

3. Obesity

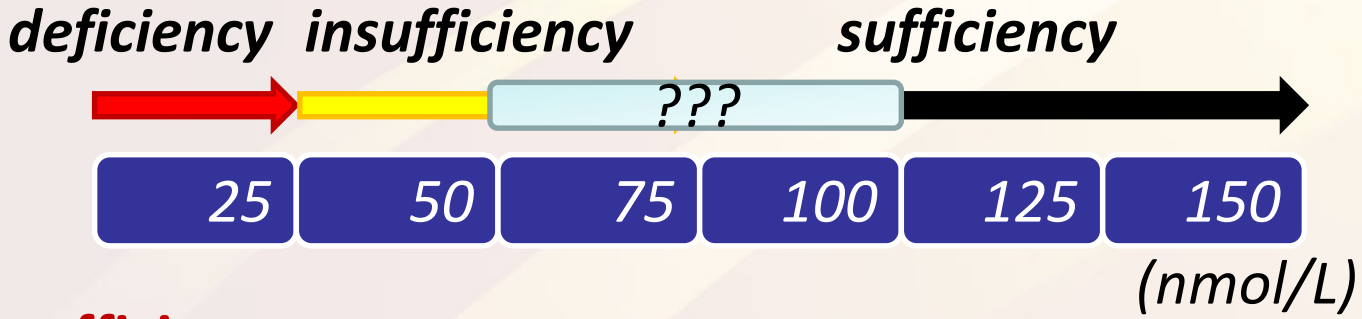
Inhibits **NF-kB** and **P38MAPK** signaling and gene transcription of **pro-inflammatory** factors

Inhibits **pro-inflammatory** cytokines and chemokines **secretion**



Nimitphongetal., 2012; Narvaezetal.2013; ShivaprakashJ.Mutt , 2014

DEFINITION OF VITAMIN D STATUS 25OHD CONTINUUM



- **Vitamin D sufficiency**:

25(OH)D = **75** – **100** nmol/L (30-40 ng/mL)

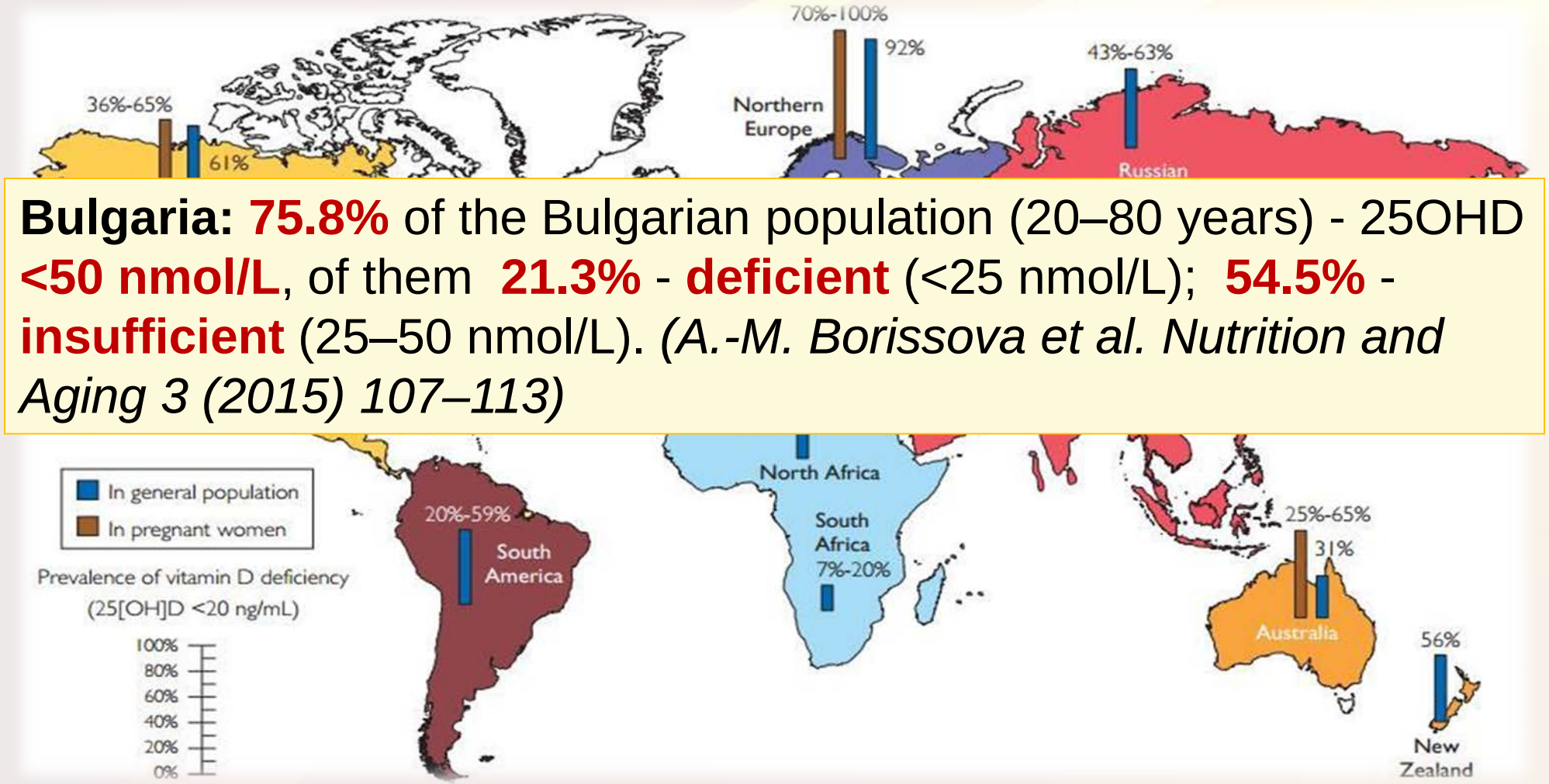
- **Vitamin D insufficiency**:

25(OH)D
- **25** – **50** nmol/L (10-20 ng/mL) – **severe**
- **50** – **75** nmol/L (20-30 ng/mL) – **low**

- **Vitamin D deficiency**:

25(OH)D < **25** nmol/L (10 ng/mL)

VITAMIN D DEFICIENCY BECOMES EPIDEMIC



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)*

Arash Hossein and Holick. Mayo Clin Proc. 2013;88(7):720-755

VITAMIN D DEFICIENCY

CAUSES

↓ synthesis:
- Melanin
- Sunscreen
- Latitude
- Winter sea

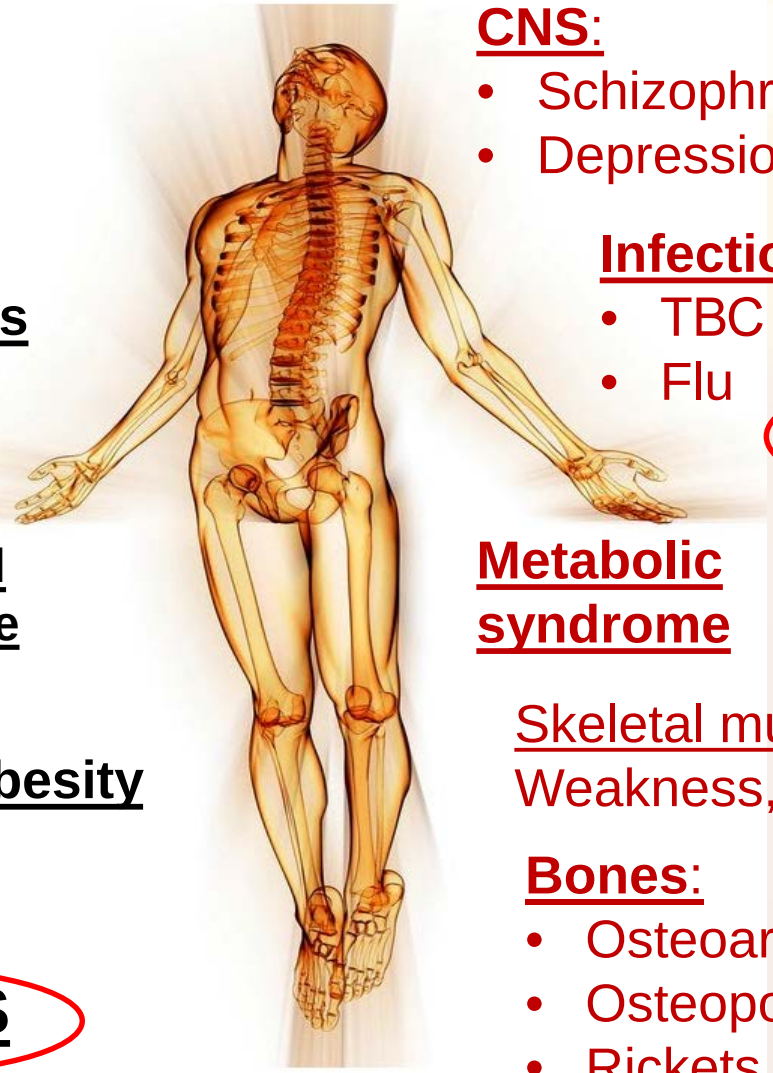
Drugs:
- Antiepileptic
- Glucocorticoids
- Tuberculostatics
- HAART

Malabsorption:
- Crohn's
- Whipple's
- Cystic fibrosis
- Celiac disease
- Cholestasis

Liver diseases

Renal failure

Obesity



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

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D and prostate cancer – our experience

Clin. Lab. 2015;61:329-335

ORIGINAL ARTICLE

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

Bistra Galunska [1], Daniela Gerova [2], Petar Kosev [3], Deyan Anakievski [3], Alexander Hinev [3]

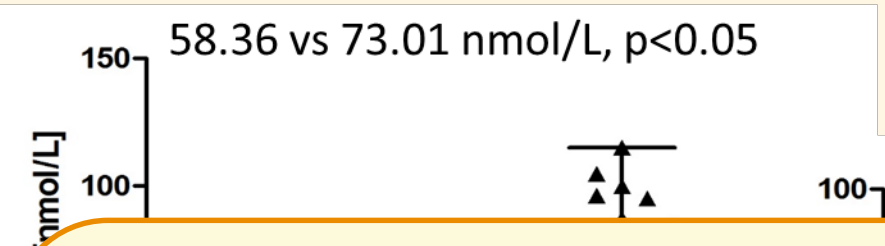
[1] *Department of Pharmaceutical Technologies, Medical University, Varna, Bulgaria*
[2] *Department of Clinical Laboratory, "St. Marina" University Hospital, Medical University, Varna, Bulgaria*
[3] *Department of Surgery, Clinic of Urology, "St. Marina" University Hospital, Medical University, Varna, Bulgaria*

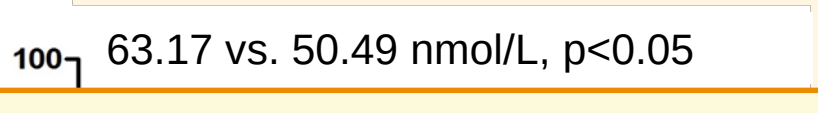
SUMMARY

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.**

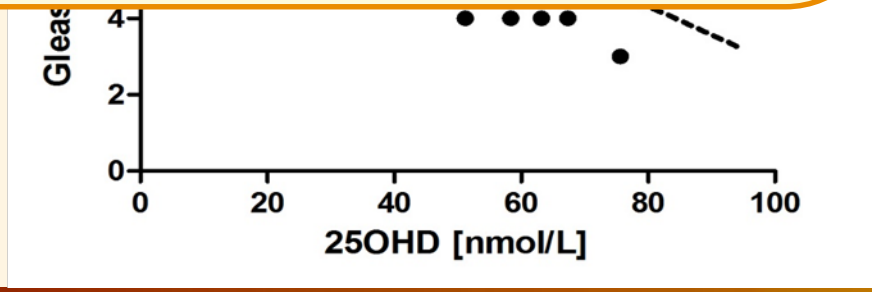
CALCITRIOL AND NON-SKELETAL HEALTH

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.**



CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D and chronic hepatitis C viral infection

Scandinavian Journal of Clinical & Laboratory Investigation, 2014; 74: 665–672

informa
healthcare

ORIGINAL ARTICLE

Prevalence of vitamin D deficiency and insufficiency in Bulgarian patients with chronic Hepatitis C viral infection

DANIELA IVANOVA GEROVA[1], BISTRA TZANEVA GALUNSKA[2], IRINA IVANOVA IVANOVA[3], ISKREN ANDREEV KOTZEV[3], TRIFON GEORGIEV TCHERVENKOV[4], SVETLOZAR PETROV BALEV[4] & DOBRIN AVRAMOV SVINAROV[5]

Departments of [1]Clinical Laboratory, [2]Pharmaceutical Sciences, [3]Internal Medicine – Clinic of Gastroenterology, and [4]Immunology, Medical University – Varna "Prof. Dr. Paraskev Stoyanov", Varna, and [5]Central Laboratory of Therapeutic Drug Management and Clinical Pharmacology, Alexandrovska University Hospital, Medical University of Sofia, Sofia, Bulgaria

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/

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D and HCV infection – our experience

- 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;

$n = 83$; NR, non-responders (patients who did not achieve at least 2 $\log_{10}$ reduction of HCV RNA at week 12 of therapy), $n = 8$; Relapsers, patients negative for HCV RNA at the end of therapy and with recurrence of HCV RNA during the 6 month follow-up, $n = 31$. Data are given as median and 25th–75th percentile. Mann-Whitney test was used for statistical analysis, $p < 0.01$.

(5.6 $\log_{10}$ IU/mL); $n = 184$ for HCV RNA < 5.6 $\log_{10}$ IU/mL and $n = 112$ for HCV RNA > 5.6 $\log_{10}$ IU/mL. Data are given as a median and 25th–75th percentile. Mann-Whitney test was used for statistical analysis. 25OHD for HCV RNA < 5.6 $\log_{10}$ IU/mL vs. 25OHD for HCV RNA > 5.6 $\log_{10}$ IU/mL, $p < 0.01$.

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D and acute diarrhea in toddlers – our experience

Integrative Food, Nutrition and Metabolism

oat open access text

Research Article ISSN: 2056-8339

Vitamin D_3 status in children with acute diarrhea

Mileva S[1*], Galunska B[2], Gospodinova M[1], Gerova D[3], and Svinarov D[4]

[1]Department of Infectious Diseases, Medical University of Varna, Bulgaria

[2]Department of Pharmaceutical Sciences, Medical University of Varna, Bulgaria

[3]Department of General Medicine, Medical University of Varna, Bulgaria

[4]Central Laboratory of TDM and Clinical Pharmacology, Alexander Hospital, Sofia, Bulgaria

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 mas-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

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D status and acute diarrhea in toddlers – our experience

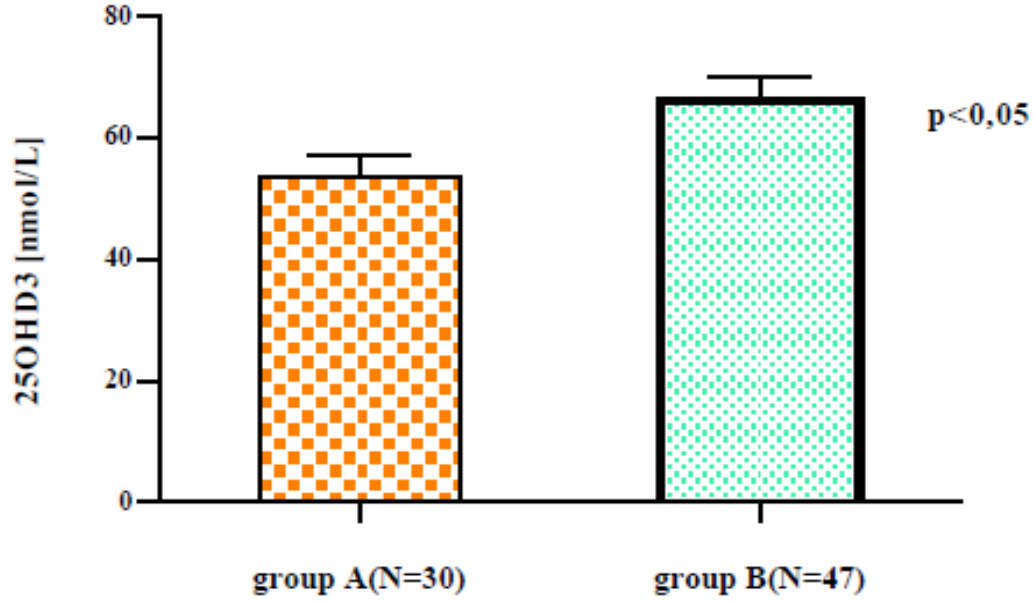


Figure 1. Mean 25OHD3 levels in patients with (group A) and without risk factors for severe diarrhea (group B).

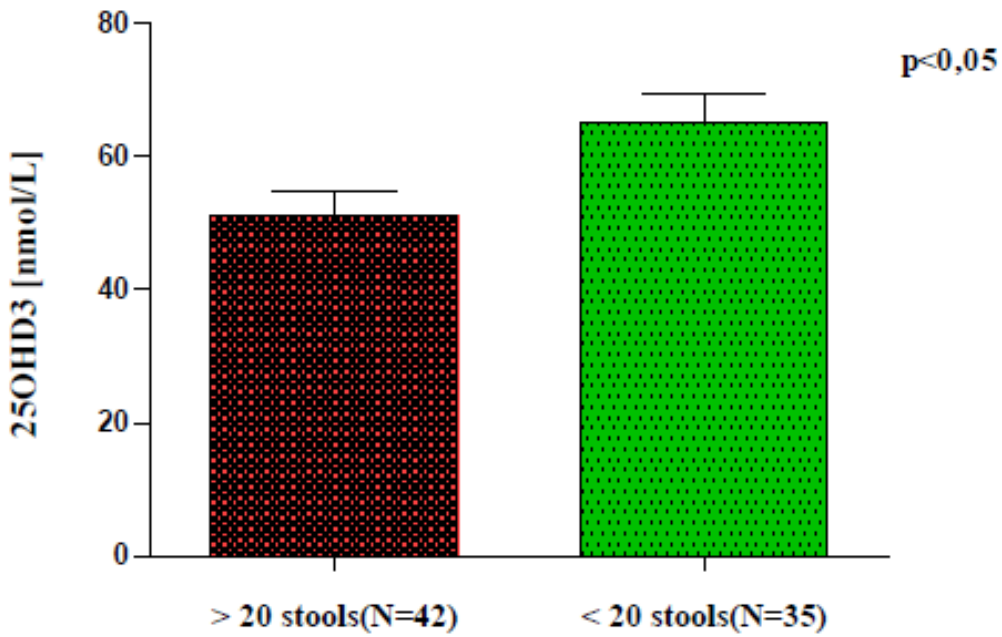


Figure 3. Mean serum 25OH vitD3 in patients with different diarrhea intensity.

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D status and obesity in children – our experience

International Journal of Research in Medical Sciences
Galunska BT et al. Int J Res Med Sci. 2016 Feb;4(2):361-368
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20160284

Research Article

Association between vitamin D status and obesity in Bulgarian pre-pubertal children: a pilot study

Bistra T. Galunska[1]*, Daniela I. Gerova[2], Sonya V. Galcheva[3], Violeta M. Iotova[3]

[1]Department of Biochemistry, Molecular medicine and Nutrigenomics, Medical University of Varna, Bulgaria
[2]Department of General Medicine and Clinical Laboratory, Medical University of Varna, Bulgaria
[3]Department of Pediatrics, Medical University of Varna, Bulgaria

Received: 29 December 2015
Revised: 04 January 2016
Accepted: 19 January 2016

***Correspondence:**
Dr. Bistra T. Galunska,
E-mail: bistra.galunska@gmail.com

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

Keywords: 25-hydroxyvitamin D, Pre-pubertal children, Obesity, Insulin resistance

CALCITRIOL AND NON-SKELETAL HEALTH

Vitamin D status and obesity in children – our experience

- **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.**

Dawson WJ. Med Probl Perform Art 2010; 25(2):49-53.

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

Funding

- BNSF, Ministry of Education, Bulgaria
- Fund “Science”, Medical University - Varna

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

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