Surrogate Markers of Vitamin D Deficiency Diagnosis

Thesis
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By

Dina Ahmed Marawan
M.B, B.CH

Supervised by

Prof Dr. /Raef Malak Boutros
Professor of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Ass.Dr. /Rania Sayed Abd EL-Baky
Assistant Professor of Internal Medicine,
Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Dr. /Laila Mahmoud Ali Hindawy
Lecturer of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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Abb.	Full term
1, 25(OH)$_2$ D ..... :	1,25-dihydroxyvitamin D
25 OHD ..... :	25 hydroxy vitamin D
ALP ..... :	Alkaline phosphatase
ALS..... :	***Amyotrophic lateral sclerosis***
BMI ..... :	Body mass index
Ca BP ..... :	Calcium binding protein
COPD ..... :	***Chronic obstructive pulmonary disease***
CVD..... :	Cardiovascular disease
DBP ..... :	Vitamin D Binding Protein
ESRD..... :	End Stage Renal Disease
FAS..... :	Fatty acid synthase
FFA..... :	Free Fatty Acids
FGF ..... :	***Fibroblast growth factors***
GFR..... :	Glomerular Filtration Rate
HDL..... :	High Density Lipoprotein
HPT ..... :	Hyperparathyroidism
IBD ..... :	***Inflammatory bowel disease***
IU ..... :	International Unit
MRSA..... :	Methicillin-resistant Staphylococcus aureus
MS..... :	Multiple Sclerosis
NHANES..... :	National Health and Nutrition Examination Survey
NIDDM ..... :	Non Insulin dependant diabetes mellitus
OPG..... :	Osteoprotegerin
PMCA1 ..... :	Plasma membrane calcium ATPase
PTH ..... :	Parathyroid hormone
RA..... :	Rheumatoid Arthritis
RANKL ..... :	Receptor activator of NF-KB Ligand
RDA..... :	Recommended Dietary Allowance
ROC curve..... :	Receiver Operating Characteristic curve

List of Abbreviations

Abb.	Full term
RXR..... :	Retinoic acid X receptor
SAD ..... :	Seasonal affective ***disorder***
SENECA ..... :	Survey in Europe on Nutrition and the Elderly; a Concerted Action
SPF ..... :	Sun Protection Factor
T1DM ..... :	Type 1 Diabetes Mellitus
TB ..... :	Tuberculosis
Th1,2..... :	T helper 1,2
UVB ..... :	ultraviolet B (shortwave) ***rays***
VDBP..... :	Vitamin D Binding Protein
VDDR..... :	Vitamin D deficiency rickets
VDI ..... :	Vitamin D intoxication
VDR..... :	Vitamin D Receptor
VDREs ..... :	Vitamin D response elements

INTRODUCTION

Vitamin D deficiency is becoming endemic in many parts of the world for different reasons; in northern countries above latitude 40°, there is insufficient UVB exposure year round, in southern and sunny countries, urbanization and traditional clothing prevents UVB reaching skin surface. As a result, wide prevalence of Vitamin D deficiency is observed world wide.

Hypovitaminosis - D is very common in Middle East & Africa and does not spare the pediatric age ***(Fuleihan, 2009).*** A large proportion of adolescent girls, up to 70% in Iran ***(Moussavi et al., 2005)***, 80% in Saudi Arabia ***(Siddiqui, Kamfar, 2007)*** & 32% in Lebanese girls and between 9% and 12% in Lebanese adolescent boys ***(Fuleihan et al., 2006).*** It was 35% for a Vitamin D level below 25 nmol/L in a study of elderly subjects from a geriatric hospital in Israel and between 60% and 65% in Lebanon, Jordan, and Iran ***(Hashemipour et al., 2006)*** and was 48% from Tunisia ***(Meddeb et al., 2005).*** Studies from Saudi Arabia, Kuwait, United Arab Emirates, and Iran reveal that 10–60%of mothers and 40–80% of their neonates had undetectable low Vitamin D levels (0–25 nmol/L) at delivery ***(Ainy et al., 2006).***

Pilot Studies about the prevalence of Vitamin D in Egypt reveal that; in fertile females between (20-50)ys the rate is 80% in Cairo ***(Matar, 2011)*** and 70% in port-Fouad ***(El- Dawoody, 2011),*** in old age between (60-70)ys the rate is more than 50%

(Selim, 2011) and 90% in those over 75ys ***(Salem, 2011)*** and in pregnant females receiving Vitamin D and calcium supplementation the rate is 50 % ***(Nady, 2011).***

Vitamin D deficiency and insufficiency are becoming more common in developed countries; in the UK, the prevalence of Vitamin D deficiency in all adults is around 14.5%, and may be more than 30% in those over 65 years old, and as high as 94% in otherwise healthy south Asian adults ***(Cheetham et al., 2010).***

In U.S population the prevalence is 40%; 32% of doctors and medical school students, 42% of African American women of childbearing age, Up to 80% of nursing home patients are vitamin-D deficient, Up to 60% of all hospital patients& 76% of pregnant mothers are severely vitamin-D deficient causing widespread vitamin-D deficiencies in their unborn children ***(Michael Holick, 2011).***

Hypovitaminosis- D is typically diagnosed by measuring the concentration of 25-hydroxyvitamin D (calcidiol) in blood, which is a precursor to the active form 1,25-dihydroxyvitamin D (calcitriol). The following are four categories for Hypovitaminosis D:

- Insufficient 50–75 nmol/L (20–30 ng/mL)
- Mild deficiency 25–50 nmol/L (10–20 ng/mL)
- Moderate deficiency 12.5–25.0 nmol/L (5–10 ng/mL)

- Severe deficiency < 12.5 nmol/L (< 5 ng/mL) ***(Australian Family Physician, 2008).***

A discrepancy exists between the cost of diagnosis of vit.D deficiency and the cost of treatment. For example; measurement of 25(OH) vit D costs about 600 EGP **(**100Dollars), on the other hand the cost of 1 injection of 200, 000IU of vit D is 5EGP (10 cents). Because of the high prevalence of Vitamin D deficiency according to pilot Egyptian study and because of the high cost of diagnosis, surrogate markers are needed to identify the individuals who need Vitamin D supplements.

AIM OF THE WORK

We aim to investigate markers of Vitamin D deficiency applicable in large sectors of society at low cost to diagnose such a widely prevalent condition with reasonable cost benefit ratio.

VITAMIN D PHYSIOLOGY AND STRUCTURE

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger Vitamin D synthesis ***(Institute of Medicine, 2010).***

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts ***(Cranney et al., 2007).***

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation ***(Holick, 2006)***. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by Vitamin D ***(Institute of Medicine, 2010).***

Several forms (vitamers) of Vitamin D exist (see table). The two major forms are Vitamin D_2 or ergocalciferol, and Vitamin D_3 or cholecalciferol, Vitamin D without a subscript refers to either D_2 or D_3 or both. These are known collectively as calciferol ***(Dorland's Illustrated Medical Dictionary, 2013)***.

Table (1): Forms of Vitamin D ***(Dorland's Illustrated Medical Dictionary, 2013):***

Name	Chemical composition
Vitamin D_1	Molecular compound of ergocalciferol with lumisterol
Vitamin D_2	Ergocalciferol (made from ergosterol)
Vitamin D_3	Cholecalciferol (made from 7-Dehydrocholesterol in the skin).
Vitamin D_4	22-dihydroergocalciferol
Vitamin D_5	Sitocalciferol (made from 7-dehydrositosterol)

Sources of Vitamin D

The main sources of Vitamin D are sunlight, supplements and diet (***Holick, 2007***). Exposure of human skin to solar UVB radiation (wavelengths: 290–315 nm) leads to the conversion of 7-dehydrocholesterol to preVitamin D_3 in the skin. PreVitamin D_3 is then rapidly converted to Vitamin D_3 (cholecalciferol) by temperature- and membrane-dependent processes ***(Holick et al., 1995).***

The number of foods naturally containing Vitamin D in significant amounts is very limited. Among these are oily fish such as salmon, sardines and tuna, and oils of the liver of some fish such as cod as well as sun-exposed mushrooms ***(Holick, 2007).***

The Recommended Dietary Allowance (RDA)

The RDA for Vitamin D is listed in the table below by life stage and gender ***(Holick et al., 2011).***

Table (2): Recommended Dietary Allowance (RDA) for Vitamin D ***(Holick et al., 2011)***.

Life Stage	Age	Males mcg/day (IU/day)	Females mcg/day (IU/day)
Infants	0-12 months	400 IU	400 IU
Children and Adolescents	1-18 years	600 IU	600 IU
Adults	19-50 years	600 IU	600 IU
Adults	51-70 years	600 IU	600 IU
Adults	71 years and older	800 IU	800 IU
Pregnancy And lactation	all ages	-	1500-2000 IU

Vitamin D metabolism

Vitamin D Bioactivation

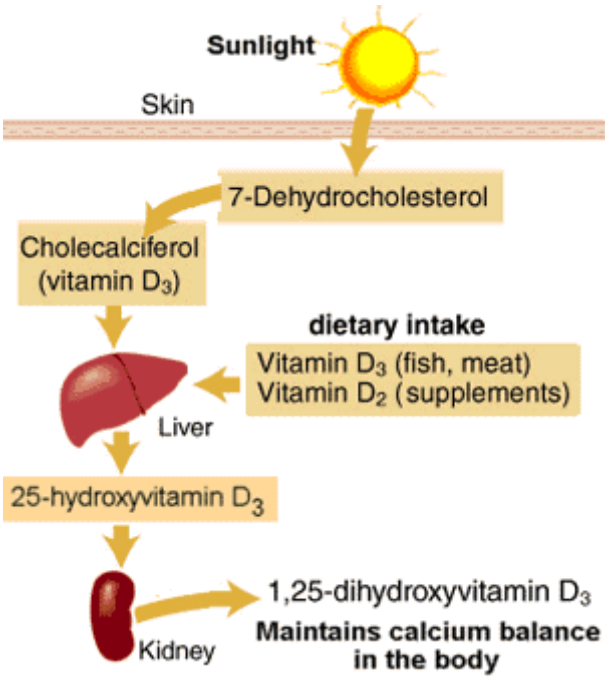

Figure (1): Steps of Vitamin D bioactivation (***Dusso et al., 2005***).

Vitamin D_2 (ergocalciferol) is obtained from certain food and, principally, from vitamin supplements. Vitamin D_3 (VD_3, cholecalciferol) is present in food and vitamin supplements, but is mainly generated by skin exposed to ultraviolet B radiation: 7- and 8-dehydrocholesterol are converted by photolysis to pre-VD_3 and then by thermal isomerization, to VD_3 ***(Dusso et al., 2005).***