Study of Indices Comprising Surrogate Markers of Vitamin D Deficiency

Thesis

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✍ Ramy Ahmed El Heggawy

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Introduction

Vitamin D deficiency is one of the most common medical conditions in recent times. It is becoming endemic in many parts of the world because of insufficient UVB exposure, urbanization, pollution and traditional clothing preventing UVB reaching skin surface. As a result, wide prevalence of vitamin D deficiency is observed in many countries.

Hypovitaminosis - D is very common in Middle East & Africa and does not spare the pediatric age *(El-Hajj et al., 2009).* A large proportion of adolescent girls, up to 70% in Iran *(Moussavi et al., 2005),* 80% in Saudi Arabia *(Siddiqui et al., 2007)* & 32% in Lebanese girls and between 9% and 12% in Lebanese adolescent boys *(El-Hajj et al., 2006).* 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 (0–10 ng/mL) at delivery *(Ainy et al., 2006).*

Pilot Studies about the prevalence of vitamin D in Egypt reveal that; the rate of hypovitaminosis - D in fertile females between (20-50) ys 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% *(Salem, 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).*

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 presents the recent levels considered important in interpretation of 25-hydroxyvitamin D levels:

- Levels <30Nmol/L (<12ng/ml) associated with vitamin D deficiency, leading to rickets in children and osteomalacia in adults.
- Levels from 30-50 Nmol/L (12-20 ng/ml) are generally considered inadequate for bone and overall health in healthy individuals.
- Levels≥50 Nmol/L (≥20ng/ml) are generally considered adequate for bone and overall health in healthy individuals.
- Levels >125Nmol/L (>50ng/ml) are emerging evidence links potential adverse effects to such high levels, particularly > 150 Nmol/L (>60 ng/ml).

(Institute of medicine, 2010)

- Vitamin D deficiency is defined as a 25 (OH) D below 20 ng/ml (50 nmol/liter).
- Vitamin D insufficiency as a 25 (OH) D of 21–29 ng/ml (52.5–72.5) nmol/liter.

(Holick et al., 2011)

Aim of the Work

A discrepancy exists between the cost of diagnosis of vitamin D deficiency and the cost of treatment. For example; measurement of 25 (OH) vitamin D costs about 500 - 600 EGP, on the other hand the cost of 1 injection of 200,000 IU of vitamin D is 10 EGP. Because of the high prevalence of vitamin D deficiency and because of the high cost of diagnosis, surrogate markers are needed to identify the individuals who need vitamin D supplements.

We aim to investigate markers of vitamin D deficiency applicable in large sectors of society at low cost and find a vitamin D deficiency index 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 is important for general good health, and researchers now are discovering that vitamin D may be important for many other reasons outside of good bone health. Some of the functions of the body that vitamin D helps with include:

- Immune system, which helps to fight infection
- Muscle function
- Cardiovascular function, for a healthy heart and circulation
- Respiratory system –for healthy lungs and airways
- Brain development
- Anti-cancer effects

(Feldman et al., 2011)

Table (1): Forms of vitamin D:

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)

Several forms (vitamers) of vitamin D exist (see table1). 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)*.

Sources of vitamin D

The two main ways to get vitamin D are by exposing bare skin to sunlight and by taking vitamin D supplements. It's hard to get the right amount of vitamin D that body needs from food.

The most natural way to get vitamin D is by exposing bare skin to sunlight (ultraviolet B rays). This can happen very quickly, particularly in the summer.No need to tan or burn skin to get vitamin D. It's just by exposing bare skin for half the time it takes for skin to turn pink and begin to burn. How much vitamin D is produced from sunlight depends on the time of day, location and the skin color. The

more skin exposed the more vitamin D is produced *(Holick, 2004).*

Factors affecting cutaneous production of vitamin D3:

- The amount of skin exposed: The more skin exposed, the more vitamin D produced.

- Age: skin production of vitamin D inversely related to age.

- Sunscreen: Sunscreen blocks a lot of vitamin D production.

- The altitude: The sun is more intense on top of a mountain than at the beach. This means more vitamin D production at higher altitudes.

- Weather: Less UVB reaches skin on cloudy days and so less vitamin D production.

- Air pollution: Polluted air soaks up UVB or reflects it back into space.

- Glass barriers: Glass blocks all UVB, skin unable to produce vitamin D behind glass barriers.

- Melanin pigment: Melanin protects against skin damage from too much UVB exposure, so darker skins with more melanin allow less UVB to enter the skin. With less UVB getting through the skin, less vitamin D is produced each minute *(Holick & Chen, 2010).*

Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D_3 and its metabolite 25 (OH) D_3. Some mushrooms provide vitamin D_2 in variable amounts. Mushrooms with enhanced levels of vitamin D_2 from being exposed to ultraviolet light under controlled conditions are also available *(USDA, Agricultural Research Service, 2011)*

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.

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