



Assessment of Vitamin D status in Healthy Egyptian Pre-pubertal Children

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

لَسْبَدَانِكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

Abb.	Full term
7-DHC.....	7-dehydrocholesterol
AAP.....	American academy of pediatrics
ALP.....	Alkaline phosphatase
ARI.....	Acute respiratory infection
BMI.....	Body mass index
CF.....	Cystic fibrosis
CFF.....	Cystic fibrosis foundation
CKD.....	Chronic kidney disease
DBP.....	Vitamin D binding protein
ELISA.....	Enzyme-linked immune sorbent assay
ESPGHAN.....	European society for pediatric gastroenterology,
GH.....	Growth hormone
ILGF1.....	Insulin like growth factor 1
IOM.....	Institute of medicine
KDOQI.....	Kidney diseases outcomes quality initiative
LD.....	Linkage disequilibrium
MED.....	Minimal erythematous dose
NHANES.....	National health and nutrition examination survey
OTC.....	Over the counter
P.....	Phosphorus
PES.....	Pediatric endocrine society
PTH.....	Parathyroid hormone
RCT.....	Randomized controlled trial
RFLPs.....	Restriction fragment length polymorphisms
SDS.....	Standard deviation scores
TMP.....	Tetramethylbenzidine
UTR.....	Untranslated region
UV.....	Ultra violet
VDR.....	Vitamin D receptor

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INTRODUCTION

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, 2011*).

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)₂D], also known as calcitriol (*Institute of Medicine, 2011*).

Vitamin D and its metabolites have a significant clinical role because of their inter-relationship with calcium homeostasis and bone metabolism. Vitamin D deficiency is common in infants who are dark skinned and exclusively breastfed beyond six months of age (*Greer et al., 2006*), particularly if there are additional risk factors such as lack of sun exposure (*Binkley et al., 2007*), maternal vitamin D deficiency during pregnancy or prematurity (*Greer, 2001*). Vitamin D deficiency is also common among children who use anticonvulsant or antiretroviral medications (*Lehmann et al., 2000*), or those with malabsorptive conditions (*Pazianas et al., 2005*). Subclinical vitamin D

deficiency, as measured by low serum 25(OH)D, is very common (*Forrest and Stuhldreher, 2001*).

Very few foods naturally contain vitamin D (fatty fish livers are the exception); dermal synthesis is the major natural source of the vitamin. Pre-vitamin D₃ is synthesized nonenzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet (UV) rays in sunlight. Previtamin D₃ undergoes a temperature-dependent rearrangement to form vitamin D₃ (cholecalciferol) (*Haddad, 1992*). The length of daily exposure required to obtain the sunlight equivalent of oral vitamin D supplementation is difficult to predict on an individual basis and varies with the skin type, latitude, season, and time of day (*Binkley et al., 2007; Terushkin et al., 2010*). Prolonged exposure of the skin to sunlight does not produce toxic amounts of vitamin D₃ because of photoconversion of previtamin D₃ and vitamin D₃ to inactive metabolites (lumisterol, tachysterol, 5,6-transvitamin D, and suprasterol 1 and 2) (*Holick et al., 1981; Holick, 2003*).

The plasma 1,25-dihydroxyvitamin D concentration is a function both of the availability of 25(OH)D and of the activities of the renal enzymes 1- α -hydroxylase and 24- α -hydroxylase (*Christakos et al., 2010*).

The estimated adequate intake for infants up to 12 months is 400 international units (10 mcg) daily. The Lawson Wilkins Pediatric Endocrine Society also recommends

supplementation with 400 international units daily of vitamin D beginning within days of birth for infants who are exclusively breast-fed (*Misra et al., 2008*).

Subclinical vitamin D deficiency may contribute to the burden of chronic diseases, particularly osteomalacia, osteoporosis, and decreased physical performance, and possibly cancer, cardiovascular disease, type 2 diabetes, and infectious and autoimmune disorders (*Holick et al., 2011*).

AIM OF THE WORK

The study aims to:

- Evaluate 25OHD status in healthy pre-pubertal Egyptian children
- Estimate the frequency of vitamin D insufficiency and deficiency among them.
- Relate 25OHD to anthropometric parameters in those children.

Chapter 1

VITAMIN D

Background

Vitamin D compounds are fat soluble sterols which are essential for the absorption and utilization of calcium and phosphorus (in the form of inorganic phosphate) in the body to maintain normal calcification of the skeleton and bone mineralization (*Shipkowski et al., 2018*).

Along with parathyroid hormone (PTH) the active form of vitamin D (25 – OHD) regulates serum calcium concentration by altering serum calcium and inorganic phosphate blood levels as needed. It maintains neuromuscular function and various other cellular processes, including the immune system and insulin production (*Allgrove, 2015*).

Physiology

Our bodies obtain vitamin D in 2 different ways. The primary source of vitamin D₃ (cholecalciferol) comes from direct synthesis in our skin (>90%). Upon exposure to ultraviolet radiation, 7-dehydrocholesterol in our epidermal cells synthesizes vitamin D₃. The remainder of our need is typically obtained from dietary sources in either form, vitamin D₃ or vitamin D₂ (ergo-calciferol). Both forms undergo hydroxylation in the liver to create the storage form of vitamin

D, 25-hydroxy vitamin D (25(OH)-D, calcidiol, or calcifediol). Furthermore, in the kidneys, hydroxylation of calcidiol synthesizes the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)-D) (calcitriol) (*Lee et al., 2013*).

Calcitriol is responsible for increasing calcium absorption, bone resorption, and decreasing renal calcium and phosphate excretion to maintain bone health (*Bikle, 2014*).

The synthesis of calcitriol is mediated by PTH, serum phosphate concentration, and growth hormone, and may occur in non-renal sites, such as alveolar macrophages and osteoblasts (*Hewison, 2012*).

Additionally, vitamin D has extraskeletal responsibilities, with vitamin D receptors in the small intestine, colon, osteoblasts, activated T and B lymphocytes, beta islet cells, and major organs (brain, heart, skin, gonads, prostate, breast, and mononuclear cells). The immunologic effects of vitamin D have stimulated great interest, but studies in these areas are currently limited in pediatric patients (*Hewison, 2012*).