

**A study of vitamin D supplementation to  
patients with chronic diseases admitted to Ain  
Shams University Hospital**

*Thesis*

**Submitted for Partial Fulfillment of Master Degree  
In Endocrinology**

*By*

**Mariam Michel Ayad Grace**  
(M.B.,B.Ch.)

*Supervised by*

**Prof. Dr. Raef Malak Botros**

Professor of Internal Medicine, Diabetes and Endocrinology  
Faculty of Medicine - Ain Shams University

**Dr. Ahmed Mohamed Bahaa El Din**

Assistant Professor of Internal Medicine, Diabetes and  
Endocrinology  
Faculty of Medicine - Ain shams University

**Dr. Hany Khairy Mansour**

Lecturer of Internal Medicine, Diabetes and Endocrinology  
Faculty of Medicine - Ain shams University

Faculty of Medicine  
Ain Shams University  
2020

## List of Contents

Title	Page
▪ List of Abbreviations.....	I
▪ List of Tables.....	IV
▪ List of Figures.....	VII
▪ Introduction.....	1
▪ Aim of the Work.....	6
▪ Review of Literature	
- Chapter (1): Vitamin D .....	7
- Chapter (2): Vitamin D Deficiency in the Hospitalized Patients.....	60
▪ Subjects and Methods.....	86
▪ Results .....	96
▪ Discussion .....	118
▪ Summary.....	126
▪ Conclusion and Recommendations .....	128
▪ References.....	129
▪ Arabic Summary.....	--

## List of Abbreviations

<b>1,25(OH)<sub>2</sub>D</b>	.....	1, 25-dihydroxyvitamin D
<b>ALB</b>	.....	Albumin
<b>ALK.P</b>	.....	Alkaline phosphatase
<b>ALT</b>	.....	Alanine aminotransferase
<b>AST</b>	.....	Aspartate aminotransferase
<b>BUN</b>	.....	Blood urea nitrogen
<b>Ca</b>	.....	Calcium
<b>CCA</b>	.....	Cholangiocarcinoma
<b>CHF</b>	.....	Congestive heart failure
<b>CLD</b>	.....	Chronic liver disease
<b>COPD</b>	.....	Chronic obstructive pulmonary disease
<b>Cr</b>	.....	Creatinine
<b>CVD</b>	.....	Cardio vascular disease
<b>CVS</b>	.....	Cerebrovascular stroke
<b>CYP</b>	.....	Cytochrome P
<b>CYP24A1</b>	.....	Cytochrome P450, family 24, subfamily A, polypeptide1
<b>CYP27B1</b>	.....	Cytochrome P450, family 27, subfamily B, polypeptide1
<b>CYP2R1</b>	.....	Cytochrome P450, family 2, subfamily R, polypeptide1
<b>DBP</b>	.....	Vitamin D binding protein
<b>DHCR7</b>	.....	7-dehydrocholesterol reductase
<b>DM</b>	.....	Diabetes Mellitus
<b>DNA</b>	.....	Deoxyribonucleic acid
<b>FEV</b>	.....	Forced expiratory volume
<b>FGF23</b>	.....	Fibroblast growth factor 23
<b>FVC</b>	.....	Forced vital capacity

## List of Abbreviations (Cont.)

<b>Gc-globulin</b> .....	Group-specific component
<b>GWAS</b> .....	Genome-wide association study
<b>HCC</b> .....	Hepatocellular carcinoma
<b>HF</b> .....	Heart failure
<b>HGB</b> .....	Hemoglobin
<b>HS</b> .....	Highly significant
<b>IBD</b> .....	Inflammatory bowel disease
<b>IL</b> .....	Interlukin
<b>IU</b> .....	International unit
<b>KDa</b> .....	kilodalton
<b>Mg</b> .....	Magnesium
<b>MMP</b> .....	Matrix metalloproteinase
<b>MS</b> .....	Multiple sclerosis
<b>NAFLD</b> .....	Non-alcoholic fatty liver disease
<b>NASH</b> .....	Non-alcoholic steato-hepatitis
<b>NT-proANP</b> .....	N-terminal pro-ANP
<b>NF- <math>\kappa</math>B</b> .....	Nuclear factor kappa B
<b>OPG</b> .....	Osteoprotegerin
<b>PBC</b> .....	Primary biliary cirrhosis
<b>PO4</b> .....	Serum Phosphorous
<b>PTH</b> .....	Parathyroid hormone
<b>r</b> .....	Pearson correlation coefficient
<b>RANKL</b> .....	Receptor activator of nuclear factor kappa-B ligand

## **List of Abbreviations** (Cont.)

<b>RAS</b> .....	Renin-Angiotensin system
<b>RCT</b> .....	Randomized controlled trial
<b>RXR</b> .....	Retinoic acid X receptor
<b>SAPS</b> .....	Simplified Acute Physiologic Scores
<b>SD</b> .....	Standard deviation
<b>T.Bil</b> .....	Total bilirubin
<b>TLR</b> .....	Toll-like receptor
<b>T.prot</b> .....	Total proteins
<b>T1DM</b> .....	Type 1 diabetes mellitus
<b>TNF</b> .....	Tumour necrosis factor
<b>VDI</b> .....	Vitamin D intoxication
<b>VDR</b> .....	Vitamin D receptor
<b>VDRE</b> .....	Vitamin D response element

## List of Tables

Table No.	Title	Page
<b>Table (1):</b>	Forms of vitamin D.....	12
<b>Table (2):</b>	Key differences in sunlight and dietary supply as contributors to vitamin D nutritional status .....	16
<b>Table (3):</b>	Tissues that express the vitamin D receptor for the steroid hormone 1 $\alpha$ , 25-dihydroxyvitamin D3.....	21
<b>Table (4):</b>	Circulating concentrations of 25-hydroxyvitamin D [25(OH)D] by vitamin D nutritional status .....	23
<b>Table (5):</b>	Recommended Dietary Allowances (RDAs) for Vitamin D .....	23
<b>Table (6):</b>	Roles of vitamin D identified in the early 20th century.....	28
<b>Table (7):</b>	VDR - dependent systems .....	35
<b>Table (8):</b>	Causes of Vitamin D Deficiency .....	42
<b>Table (9):</b>	Selected vitamin D supplementation guidelines published since 2010.....	57
<b>Table (10):</b>	Vitamin D deficiency and disease association.....	64
<b>Table (11):</b>	Reference values of vitamin D levels ....	92
<b>Table (12):</b>	Baseline characteristic of patients in intervention and control groups.....	98
<b>Table (13):</b>	Vitamin D level in the studied groups upon admission .....	99

## List of Tables (Continued)

Table No.	Title	Page
<b>Table (14):</b>	Comparison of outcomes regarding mortality in patients of control and intervention group.....	100
<b>Table (15A):</b>	Multivariable binary logistic regression analysis for the relation between Vitamin D supplementation and mortality as adjusted for the disease status and baseline vitamin D status .....	102
<b>Table (15B):</b>	Multivariable binary logistic regression analysis for the relation between Vitamin D supplementation and mortality as adjusted for the disease status and baseline vitamin D level.....	103
<b>Table (16):</b>	Comparison of baseline characteristics of patients with CLD in control and intervention groups .....	104
<b>Table (17):</b>	Comparison of outcome in patients with CLD in control and intervention groups.....	106
<b>Table (18):</b>	Comparison of baseline characteristics of patients with CHF in control and intervention groups.....	108
<b>Table (19):</b>	Comparison of outcome in patients with CHF in control and intervention groups.....	110

## List of Tables (Continued)

Table No.	Title	Page
<b>Table (20):</b>	Comparison of baseline characteristics of patients with CLD or CHF in intervention group.....	113
<b>Table (21):</b>	Comparison of outcome in patients with CLD or CHF in intervention group .....	114
<b>Table (22):</b>	Comparison of baseline characteristics of patients with CLD or CHF in control group.....	115
<b>Table (23):</b>	Comparison of outcome in patients with CLD or CHF in control group .....	116



## List of Figures

Figure No.	Title	Page
<b>Fig. (1):</b>	The structures of vitamin D2 and vitamin D3 .....	13
<b>Fig. (2):</b>	Biosynthesis of vitamin D .....	15
<b>Fig. (3):</b>	Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism .....	26
<b>Fig. (4):</b>	The mechanism of action of 1,25(OH) <sub>2</sub> D in various target cells .....	36
<b>Fig. (5):</b>	Risk factors of low vitamin D status ....	41
<b>Fig. (6):</b>	Clinical Features of Rickets .....	49
<b>Fig. (7):</b>	A schematic representation of the major causes for vitamin D deficiency and potential health consequences .....	52
<b>Fig. (8):</b>	Vitamin D effects on heart and blood vessels .....	75
<b>Fig. (9):</b>	Potential antihypertensive effects of vitamin D .....	77
<b>Fig. (10):</b>	Outcome in patients of control and intervention groups .....	100
<b>Fig. (11):</b>	Survival in patients of control and intervention groups .....	101
<b>Fig. (12):</b>	Outcome in patients in control and intervention groups stratified by the chronic illness .....	109

## List of Figures (Continued)

Figure No.	Title	Page
<b>Fig. (13):</b>	Outcome in control and intervention groups stratified by the chronic illness .....	110
<b>Fig. (14):</b>	Outcome in patients with CLD or CHF as stratified by the intervention ...	114
<b>Fig. (15):</b>	Survival in patients with CLD or CHF as stratified by the intervention ...	115

## Abstract

**Background:** Vitamin D deficiency and insufficiency have become a common problem worldwide. Vitamin D has been associated with all causes of mortality in chronic diseases and associated with a longer hospital stay and poor outcome. **Aim of the Study:** to evaluate the role of vitamin D supplementation on the outcome of hospitalization for patients with CLD or CHF admitted to Ain Shams University Hospitals (ASUH) with acute deterioration of their illness. **Subjects and methods:** We conducted prospective case control on 80 patients collected from inpatient ward of endocrinology, divided into 2 groups; 40 patients with chronic liver diseases and 40 patients with heart failure. Serum 25OH-vitamin D and calcium, phosphate and PTH were measured to all participants before intervention. 20 patients of each group (Intervention group) received single dose of vitamin D within 3 days of admission and the other 20 patients of each group (control group) did not receive vitamin D. **Results:** no significant difference between patients who received vitamin D supplementation and who did not receive vitamin D supplementation as regards outcome and survival with P value 1.000 in patients with CLD and 0.823 in patients with CHF. On the other hand, we found baseline vitamin D level was an independent predictor of mortality (P value .018). **Conclusion:** We found that a beneficial effect of vitamin D supplementation can't be achieved with single dose vitamin D (200,000 IU) on CHF or CLD hospitalized patients' mortality. We recommend that vitamin D supplementation should be considered in CLD and CHF outpatients, with exception of hypercalcemic and hyperphosphatemic patients, as baseline vitamin D status affects the disease course and mortality prior to disease deterioration and hospitalization.

**Key words:** Vitamin D level, Vitamin D supplementation, CLD, CHF, outcome.

## INTRODUCTION

Vitamin D is the sunshine vitamin. During exposure to sunlight 7-dehydrocholesterol in the skin absorbs ultraviolet B radiation converting it to previtamin D<sub>3</sub>. Previtamin D<sub>3</sub> being thermodynamically unstable isomerizes within a few hours to form vitamin D<sub>3</sub>. A multitude of factors affect its synthesis including skin pigmentation, time of day, season, latitude, altitude, and sunscreen use. The body has a large capacity to produce vitamin D<sub>3</sub>, and sensible sun exposure can be effective in helping to maintain blood levels of 25-hydroxyvitamin D (*Holick, 2017*).

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements. Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D<sub>3</sub>, which is rapidly converted to vitamin D<sub>3</sub>. Because any excess previtamin D<sub>3</sub> or vitamin D<sub>3</sub> is destroyed by sunlight, excessive exposure to sunlight does not cause vitamin D<sub>3</sub> intoxication (*Holick and Garabedian 2006*).

Research carried out during the past two-decades extended the understanding of actions of vitamin D, from regulating calcium and phosphate absorption and bone

## ***-Introduction-***

---

metabolism to many pleiotropic actions in organs and tissues in the body. Most observational and ecological studies report association of higher serum 25-hydroxyvitamin D [25(OH)D] concentrations with improved outcomes for several chronic, communicable and non-communicable diseases (*The Journal of Steroid Biochemistry and Molecular Biology, 2018*).

After entering bloodstream, from intestinal absorption or skin synthesis, vitamin D is converted into 25-hydroxyvitamin D [25(OH)D] in the liver and then to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] in the kidneys (*Jones, 2012*).

25(OH)D and 1,25(OH)<sub>2</sub>D circulate in the blood mostly bound to vitamin D-binding protein (DBP). After a release from DBP to tissues, 1,25(OH)<sub>2</sub>D triggers through intracellular vitamin D receptor (VDR) a numerous metabolic actions throughout the body (*Kaufmann, 2014*).

In tissues, 1,25(OH)<sub>2</sub>D dissociate from DBP, and binds to intracellular vitamin D receptors (VDR), which triggers several ubiquitous metabolic actions in tissues and organs. The main function of 1,25(OH)<sub>2</sub>D is to maintain a tight calcium and phosphorus homeostasis in the circulation. This is also modulated by parathyroid hormone (PTH), and fibroblast growth factor (FGF-23) (*Weaver and Heaney, 2006*).

## ***-Introduction-***

---

Vitamin D, an essential nutrient to sustain health, is a member of the steroid nuclear hormone superfamily, and was first discovered to be able to prevent rickets in children. Further research has found that Vitamin D has broader physiological functions. Currently the biological effects of Vitamin D are divided into two categories: First, in calcium and phosphorus metabolism, considered the classical activity; and second, the non-classical or alternative pathway that mainly affects immune function, inflammation, anti-oxidation, anti-fibrosis and others, as well as inhibitory effects on the many kinds of malignancies (*Wang et al., 2017*).

Vitamin D deficiency and insufficiency is a global health issue that afflicts more than one billion children and adults worldwide. The consequences of vitamin D deficiency cannot be under estimated. There has been an association of vitamin D deficiency with a myriad of acute and chronic illnesses including preeclampsia, childhood dental caries, periodontitis, autoimmune disorders, infectious diseases, cardiovascular disease, deadly cancers, type 2 diabetes and neurological disorders (*Holick et al., 2011*).

The Endocrine Society in 2011 reported on the findings from their assembled panel of vitamin D experts. In the published Endocrine Society's Practice Guidelines

on Vitamin D, vitamin D deficiency was defined as a  $25(\text{OH})\text{D} < 20 \text{ ng/mL}$ , insufficiency as  $21\text{--}29 \text{ ng/mL}$  and sufficiency as at least  $30 \text{ ng/mL}$  for maximum musculoskeletal health (*Holick et al., 2011*).

Vitamin D deficiency and insufficiency have become pandemic and are now seen in every country in the world. It has been estimated that more than one billion people worldwide are either vitamin D deficient or insufficient (*Holick, 2017*).

Though abundant with sunshine, accumulating data from other Middle East countries indicate a prevalence of vitamin D deficiency and insufficiency. A report on the global vitamin D status published by the Scientific Advisory Committee of the IOF (International Osteoporosis Foundation) presented earlier data from some Middle East countries indicating that 70-80% of adolescent girls in Saudi Arabia and Iran had vitamin D levels of  $<25 \text{ nmol/L}$ , while in Lebanon the figure was 32% in the same age group. Studies conducted among adults indicate a prevalence of 60–65% for vitamin D values  $<25 \text{ nmol/L}$  in Lebanon, Iran and Jordan and 48% for cut-off below  $37.5 \text{ nmol/L}$  in Tunisia. Additionally, investigations in Saudi Arabia, Kuwait, the United Arab Emirates and Iran indicate that 10-60% of mothers and 40–80% of their neonates have undetectable or low 25-OH vitamin D levels ( $0\text{--}25 \text{ nmol/L}$ ) at the time of delivery (*Bassil et al., 2013*).