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

Thesis

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List of Abbreviations

1,25(OH)2D .....1, 25-dihydroxyvitamin D

ALB.....Albumin

ALK.P .....Alkaline phosphatase

ALT.....Alanine aminotransferase

AST.....Aspartate aminotransferase

BUN .....Blood urea nitrogen

Ca.....Calcium

CCA .....Cholangiocarcinoma

CHF .....Congestive heart failure

CLD .....Chronic liver disease

COPD.....Chronic obstructive pulmonary disease

Cr .....Creatinine

CVD .....Cardio vascular disease

CVS .....Cerebrovascular stroke

CYP.....Cytochrome P

CYP24A1 .....Cytochrome P450, family 24, subfamily A, polypeptide1

CYP27B1 .....Cytochrome P450, family 27, subfamily B, polypeptide1

CYP2R1 .....Cytochrome P450, family 2, subfamily R, polypeptide1

DBP .....Vitamin D binding protein

DHCR7.....7-dehydrocholesterol reductase

DM.....Diabetes Mellitus

DNA .....Deoxyribonucleic acid

FEV .....Forced expiratory volume

FGF23 .....Fibroblast growth factor 23

FVC .....Forced vital capacity

List of Abbreviations (Cont.)

Gc-globulin.....Group-specific component

GWAS .....Genome-wide association study

HCC.....Hepatocellular carcinoma

HF .....Heart failure

HGB.....Hemoglobin

HS .....Highly significant

IBD .....Inflammatory bowel disease

IL.....Interlukin

IU.....International unit

KDa .....kilodalton

Mg .....Magnesium

MMP .....Matrix metalloproteinase

MS .....Multiple sclerosis

NAFLD.....Non-alcoholic fatty liver disease

NASH.....Non-alcoholic steato-hepatitis

NT-proANP .....N-terminal pro-ANP

NF- κB.....Nuclear factor kappa B

OPG.....Osteoprotegerin

PBC .....Primary biliary cirrhosis

PO4 .....Serum Phosphorous

PTH .....Parathyroid hormone

r.....Pearson correlation coefficient

RANKL.....Receptor activator of nuclear factor kappa-B ligand

List of Abbreviations (Cont.)

RAS .....Renin-Angiotensin system

RCT .....Randomized controlled trial

RXR.....Retinoic acid X receptor

SAPS.....Simplified Acute Physiologic Scores

SD.....Standard deviation

T.Bil .....Total bilirubin

TLR .....Toll-like receptor

T.prot.....Total proteins

T1DM .....Type 1 diabetes mellitus

TNF .....Tumour necrosis factor

VDI.....Vitamin D intoxication

VDR.....Vitamin D receptor

VDRE.....Vitamin D response element

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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 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 D3. Previtamin D3 being thermodynamically unstable isomerizes within a few hours to form vitamin D3. 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_3, 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_3, which is rapidly converted to vitamin D_3, Because any excess previtamin D_3 or vitamin D_3 is destroyed by sunlight, excessive exposure to sunlight does not cause vitamin D_3 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

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 [$1,25(OH)_2D$] in the kidneys ***(Jones, 2012).***

25(OH)D and $1,25(OH)_2D$ circulate in the blood mostly bound to vitamin D-binding protein (DBP). After a release from DBP to tissues, $1,25(OH)_2D$ triggers through intracellular vitamin D receptor (VDR) a numerous metabolic actions throughout the body ***(Kaufmann, 2014).***

In tissues, $1,25(OH)_2D$ 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 $1,25(OH)_2D$ 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).***

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 wells 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(OH)D < 20 ng/mL, insufficiency as 21–29 ng/mL and sufficiency as at least 30 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 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 nmol/L in Lebanon, Iran and Jordan and 48% for cut-off below 37.5 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 (0–25 nmol/L) at the time of delivery ***(Bassil et al., 2013).***