Vitamin D Status in Egyptian Patients with Cancer: A Possible Risk Factor

Thesis

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Mahmoud Amin

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List of Abbreviations

Abb.	Full term
25(OH)2D	25-hydroxy vitamin D
C/EBPβ	Ccaat-enhancer-binding protein β
CDK	Cyclin dependent kinases (CDK)
CEA	Carcinoembryonic antigen (CEA)
DC	Dendritic cells
DINOMIT	Dysjunction–Initiation–Natural selection–Overgrowth–Metastasis–Involution–Transition
DNA	Deoxyribonucleic acid (DNA)
DRE	Digital rectal examination (DRE)
EGFR	Epidermal growth factor receptors
ER	Endoplasmic reticulum
FAP	Familial adenomatous polyposis (FAP)
FAP	Familial adenomatous polyposis (FAP)
FASL	Fas ligand.
FOBT	Faecal occult blood test (FOBT)
FXR	Farnesoid X receptor
HNPCC	Hereditary nonpolyposis colon cancer (HNPCC)
HNPCC	Hereditary non-polyposis colorectal cancer (HNPCC)
HUVEC	human umbilical vein endothelial cells
IL	Interleukin.
INF-γ	Gama interferon.
LCA	Lithocholic acid
MAPK	Mitogen-activated protein kinase
MARRS	Membrane associated, rapid response, steroid-binding
MBC	Metastatic breast cancer (MBC)
MHC	Major histocompatibility complex.
mOC	Mouse osteocalcin
MRI	Magnetic resonance imaging (MRI)
NK	Natural killer
NOD	Non-obese diabetic

List of Abbreviations (Cont…)

Abb.	Full term
PDDR	Pseudovitamin D-deficient rickets
PKC	Protein kinase C
PLA2	Phospholipase A2
PLC	Phospholipase C
PPV	Positive predictive value (PPV)
PSA	Prostate-specific antigen (PSA)
PTH	Parathyroid hormone
PXR	Pregnane X receptor
PXR	Retinoid X receptor
rOC	Rat osteocalcin
SCC	squamous cell carcinoma (SCC)
SPF	Sun protection factor
TDEC	tumor-derived endothelial cells (TDEC)
Th	T helper
TNF	Tumor necrosis factor.
UV-B	Ultra violet
VDBP	Vitamin D binding protein (VDBP)
VDR	Vitamin D receptor
VDR	Vitamin D receptor (VDR)
VDR	Vitamin D receptor.
VDREs	Vitamin D responsive elements
VSMCs	Vascular smooth muscle cells (VSMCs)

INTRODUCTION

Vitamin D is a fat-soluble vitamin that regulates calcium and bone homeostasis and also has diverse biological effects relevant to carcinogenesis. Modest amounts of vitamin D come from supplements and dietary sources such as fortified dairy products and cereals and fatty fish. However, the majority of vitamin D, up to 90%, is produced naturally in the body when UVB light hits a precursor molecule in the skin ***(Raman et al., 2011).***

In the cancer research field, vitamin D has emerged as the most prolific topic in the last decade with work connecting it with risk reduction in various epithelial cancers. Aside from calcium homeostasis, vitamin D exerts a wide range of immunogenic and antiproliferative activities in the body. Of particular interest to the oncologists is the reduced incidence of breast, colon, and prostate cancers with higher sun exposure, higher intake, or higher serum levels of vitamin D. Vitamin D exerts its antiproliferative effect by binding to vitamin D receptor (VDR) found in various tissues and cells of the body. Several human genes contain vitamin D response elements (specific DNA sequences) that encode for proteins important in regulation of cell proliferation, differentiation, apoptosis, and angiogenesis. When serum vitamin D levels are suboptimal these activities are impaired, and as a result enhanced cellular

growth, neoangiogensis, and cancer development take place ***(Grant, 2002).***

Vitamin D from both diet and sun exposure is metabolized in the liver to 25-hydroxy vitamin D (25(OH)2D) and then further hydroxylated by 1 alpha hydroxylase enzyme in kidneys and other tissues like breast cells to 1,25- dihydroxy vitamin D (1,25 (OH)2D), the most biologically active form and the natural ligand for VDR. Serum concentration of 25(OH)2D is more sensitive to exogenous sources (dietary and supplemental intake) and endogenous production (through synthesis in the skin) of vitamin D. It also has a long half-life of 3 weeks, is the predominant form of vitamin D in plasma and the major storage form; hence the circulating 25(OH)2D is the best indicator of vitamin D status of the body ***(Imtiaz et al., 2012).***

Numerous preclinical studies have shown that 1,25-(OH)2D inhibits cell proliferation, induces differentiation and apoptosis. However, several epidemiologic studies evaluating the association between vitamin D and colon or breast cancer risk have yielded inconsistent results. Some of these studies assessed the effects of dietary and supplemental intake of parentral vitamin D, inspite of the fact that vitamin D endogenous production through sunlight exposure is the major source of vitamin D in the body ***(Peters et al., 2012).*** Vitamin D deficiency is also associated with secondary hyperparathyroidism which results in increased bone

resorption, release of calcium from bones, and may precipitate or exacerbate osteoporosis. Thus, these cancer patients must undergo a baseline metabolic bone evaluation with serum vitamin D levels, serum calcium levels and parathyroid hormone (PTH) status ***(Imtiaz et al., 2012).***

AIM OF THE WORK

The aim of this work is to assess the frequency of vitamin D deficiency in Egyptian patients with colon, breast and prostate cancers, so as to determine whether these cancers are associated with vitamin D deficiency as a possible risk factor.

Chapter One

VITAMIN D

Introduction:

Vitamin D is a lipid-soluble vitamin which consists of steroid molecule structure. Vitamin D is not a pure vitamin because its requirements are not only fulfilled through consumption of food containing vitamin D but could also be synthesized by the body with the help of sun ray exposure ***(Dusso et al., 2005).***

Structure and Synthesis:

The term vitamin D is, unfortunately, an imprecise term referring to one or more members of a group of steroid molecules. Vitamin D_3, also known as cholecalciferol is generated in the skin of animals when light energy is absorbed by a precursor molecule 7-dehydrocholesterol. Vitamin D is thus not a true vitamin, because individuals with adequate exposure to sunlight do not require dietary supplementation. There are also dietary sources of vitamin D, including egg yolk, fish oil and a number of plants. The plant form of vitamin D is called vitamin D_2 or ergosterol. However, natural diets typically do not contain adequate quantities of vitamin D, and exposure to sunlight or consumption of foodstuffs purposefully

supplemented with vitamin D are necessary to prevent deficiencies ***(How et al., 1994).***

Vitamin D, as either D_3 or D_2, does not have significant biological activity. Rather, it must be metabolized within the body to the hormonally-active form known as 1, 25-dihydroxycholecalciferol. This transformation occurs in two steps, as depicted in Figure (1).

Within the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase. Within the kidney**,** 25-hydroxycholecalciferol serves as a substrate for 1-alpha-hydroxylase, yielding 1,25-dihydroxycholecalciferol, the biologically active form. Each of the forms of vitamin D is hydrophobic, and is transported in blood bound to carrier proteins. The major carrier is called, appropriately, vitamin D-binding protein. The half-life of 25-hydroxycholecalciferol is several weeks, while that of 1, 25-dihydroxycholecalciferol is only a few hours ***(How et al., 1994).***

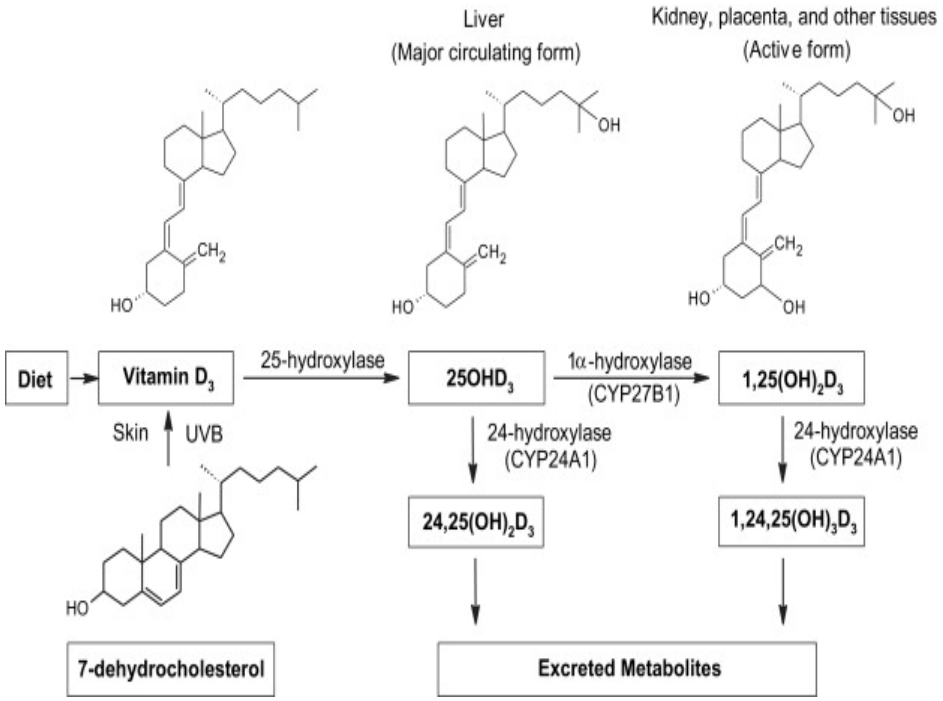

Fig. (1): Metabolism of vitamin D ***(How et al., 1994).***

Control of Vitamin D Synthesis:

Hepatic synthesis of 25-hydroxycholecalciferol is only loosely regulated, and blood levels of this molecule largely reflect the amount of vitamin D produced in the skin or ingested. In contrast, the activity of 1-alpha-hydroxylase in the kidney is tightly regulated and serves as the major control point in production of the active hormone. Interesting species differences exist in the ability to synthesize vitamin D through the sunlight-mediated pathway. The skin of humans, horses, pigs, rats, cattle and sheep contain adequate quantities of 7-dehydrocholesterol which can effectively be converted to cholecalciferol. In contrast, the skin of dogs and cats contains