The association between vitamin D level and Endometriosis

Thesis

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By

Amany Mohammed Abdullah Okashah
(M.B.,B.Ch.)
Faculty of Medicine
Tripoli University, Libya

Supervised by

Prof. Dr. Sherif Mohammed Abd El-Hamid
Professor of Obstetrics & Gynecology
Faculty of Medicine - Ain Shams University

Dr. Dina Yahia Mansour Ali
Lecturer of Obstetrics & Gynecology
Faculty of Medicine - Ain shams University

Dr. Heba-t Allah Nader El-Sayed
Fellow of Clinical Pathology
Clinical Pathology- Ain Shams University

Faculty of Medicine
Ain Shams University

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List of Abbreviations

25(OH)D ..... 25-hydroxyvitamin D
ART..... Assisted reproductive technique
ASRM..... American Society for Reproductive Medicine
BMI ..... Body mass index
CT ..... Computerized tomography
DES..... Diethylstilboesterol
DM ..... Diabetes mellitus
E1 ..... Estrone
E2 ..... Estradiol
EFI..... Endometriosis fertility index
ELISA..... Enzyme-linked immunosorbent assay
FDA..... Food and Drugs Administration
GnRH..... Gonadotropin releasing hormone
ICSI..... Intracytoplasmic sperm injection
IL ..... Interleukin
IQR ..... Interquartile range
IU..... International unit
IVF..... In vitro fertilization
MRI..... Magnetic resonance imaging
NF ..... Necrosis factor
NNT..... Number needed to treat
NSAID ..... Non-steroidal anti-inflammatory drugs
PR..... Progesterone receptor
SD..... Standard deviation
SPSS ..... Statistical package for social science
Th ..... T-helper cells
TNF..... Tumor necrosis factor
USA..... United States of America

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INTRODUCTION

The immunomodulatory, anti-inflammatory, and anti-proliferative properties of vitamin D have laid the basis for a possible function of this prohormone in the pathogenesis of endometriosis ***(Buggio et al., 2016).***

In fact, a dysfunction of the immune system responsible for a state of chronic inflammation has been claimed to play a role in the multifactorial pathogenesis of the disease ***(Sourial et al., 2014)***.

Indeed, endometriosis is characterized by a reduced T-cell cytotoxicity, a functional deficit of natural killer lymphocytes, and higher concentration of activated macrophages in the peritoneal fluid, which generate a cascade of cytokines and vascular endothelial growth factors favoring the proliferation of endometrial cells and angiogenesis ***(Osuga et al., 2011)***.

Along with this theory, abnormal levels of pro-inflammatory cytokines have been detected in the peritoneal fluid and serum of affected women, and murine models suggested the potential role of interleukin-6 and tumor necrosis factor-a through their effect on inflammatory angiogenesis ***(Lin et al., 2006)***.

Moreover, vitamin D receptor is expressed in ovarian tissue, endometrium, and fallopian epithelial cells and both eutopic and ectopic endometrium express the enzyme 1a-hydroxylase, responsible for the conversion of 25-hydroxyvitamin D [25(OH)D] into the biologically active form of vitamin D, calcitriol ***(Vigano et al., 2006)***.

Of relevance here is a recent study in a murine model of endometriosis showing that calcitriol is able to prevent both ectopic implantation of endometrium and reduce already established lesions ***(Mariani et al., 2012)***.

Finally, numerous in vitro and in vivo studies have demonstrated that vitamin D deficiency could increase the risk of several cancer and autoimmune diseases, which tend to be more common in women with endometriosis ***(Holick, 2007)***.

Given this background, the potential role of vitamin D is of increasing interest, and in the past two decades, various studies have investigated the relation between endometriosis and vitamin D serum levels, with inconsistent results ***(Anastasi et al., 2017)***.

Therefore, the influence of vitamin D on endometriosis development and progression remains to be clarified. To shed more light on this potential association, will be compared serum concentrations of 25(OH)D in women with and without endometriosis.

Aim of the Work

In women with endometriosis, the aim of this study is to assess the association between 25-Hydroxyvitamin D Serum Levels and this disease.

Study hypothesis:

In women with endometriosis, there is may be an association between 25-Hydroxyvitamin D Serum Levels and this disease.

Research question:

In women with endometriosis, is there a relation between 25-Hydroxyvitamin D Serum Levels and this disease?

Chapter (1): Vitamin D

Vitamin D is a family of fat-soluble secosteroids (i.e., steroids in which one of the bonds in the steroid rings is broken. The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2 having a double bond between carbons number 22 and 23, and a methyl group on carbon number 24) having a cornerstone role in raising intestinal absorption levels of calcium, magnesium, and phosphate, and various biological influences ***(Boron et al., 2016).***

In humans, the crucial compound in this group are vitamin D_3 (named as cholecalciferol) and vitamin D_2 (i.e ergocalciferol). Cholecalciferol and ergocalciferol could be ingested from the diet and from supplements. Only a few foods have vitamin D. The chief natural source of the vitamin is synthetic pathway of cholecalciferol in the skin from cholesterol via a chemical reaction that is dependent on sun exposure (particularly uv radiation) ***(Bischoff et al., 2012).***

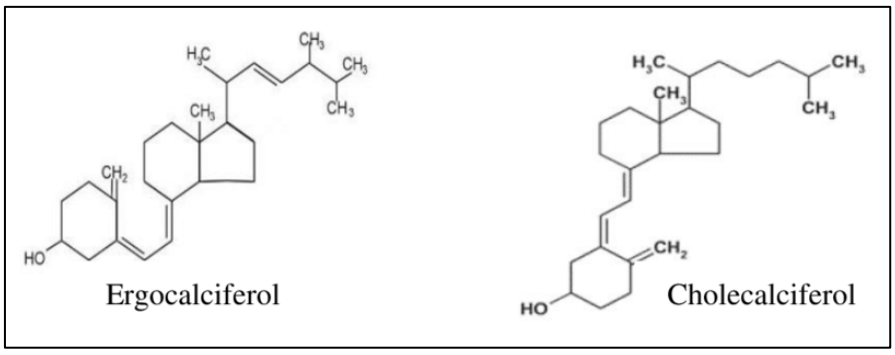

Figure (1): Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) ***(Olmos et al., 2015)***

Vitamin D from the diet or skin synthesis is an inactive biological form; enzymatic conversion (by hydroxylation reaction) in the liver and kidney is needed for active form synthesis. Interestingly it could be considered a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then triggers its effects via a nuclear receptor in multiple regions ***(Theodoratou et al., 2014).***

Cholecalciferol is converted within the liver to calcifediol (i.e 25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 1,25-dihydroxycholecalciferol) are assayed in serum to assess an individual vitamin D status. Calcifediol is additionally hydroxylated by the kidneys to form calcitriol (named as 1,25-dihydroxycholecalciferol), the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, have a crucial role regulating calcium and phosphate concentration levels, and enhancing the healthy process of growth and remodeling of bone. Calcitriol in addition has other actions involving triggering of cellular growth, neuromuscular and immunological functions, and decreasing pathological process of inflammation ***(Bjelakovic et al, 2014; Bolland et al, 2014; Pittas et al, 2010).***

Vitamin D has a considerable role in calcium homeostasis and metabolic pathways. Vitamin D supplementation is administered to manage and prevent pathological development of osteomalacia and rickets, however the research based evidence for other health

impacts of vitamin D supplementation in the general population is contradictory. The impact of vitamin D supplementation on mortality rates is not clear, with one research meta-analysis revealing a small reduction in mortality in elderly individuals, and another concluding no clear justification exists for routine recommendation of supplementation for prevention of various diseases, and that further research efforts are required in these interesting issues ***(Freedman et al., 2012).***

The two major forms are vitamin D_2 or ergocalciferol, and vitamin D_3 or cholecalciferol; collectively as calciferol. Vitamin D_2 was chemically described in 1931. In 1935, the chemical nature of vitamin D_3 was verified to be a result from ultraviolet irradiation exposure of 7-dehydrocholesterol ***(Khalid et al., 2017).***

Calcium regulation

The active vitamin D metabolite calcitriol mediate its physiological action by binding to the vitamin D receptors, which are mainly located within the nuclei of target cells. The binding of calcitriol to the vitamin D receptors permits the vitamin D receptors to take action as a transcription factor that regulates the genetic expression of transport proteins (e.g. calbindin), which are implemented in calcium absorptive action within the intestine. The vitamin D receptor is a subtype of the nuclear receptor superfamily of steroid/thyroid hormone receptors, and they are interestingly expressed by cells all over the body, e.g. brain, heart, skin, ovaries, and breast ***(Autier et al., 2014).***

Vitamin D receptor trigger within the intestine, bone, kidney, and parathyroid gland cells causes maintenance of normal calcium and phosphorus serum levels in the circulation (with the aid of parathyroid hormone and calcitonin) and to the preservation of intact bone structural composition ***(O'Connor et al., 2013).***

One of the crucial functions of vitamin D is maintenance of skeletal calcium balance by enhancing calcium absorption activity within the intestines, augmenting bone resorption by raising numbers of osteoclasts, preserving calcium and phosphate normal physiologic levels for the process of bone formation, and permitting appropriate functional activity of parathyroid hormone to sustain calcium serum levels ***(Beveridge et al., 2015).***

Vitamin D deficiency could result in decreased bone mineral density and a raised pathological risk of diminished bone density (i.e osteoporosis) or bone fracture due to lack of vitamin D influences mineral metabolic pathways within the body. Consequently, vitamin D is also crucial for structural bone remodeling process via its function as an effective stimulator of the process of bone resorption ***(Lowe et al., 2017).***

Interestingly vitamin D receptors regulate physiological and biochemical pathways of cellular proliferation and differentiation. Vitamin D impacts the immunological system, and vitamin D receptors are expressed in various white blood cells, involving monocytes

and activated T and B cells. In vitro, vitamin D was revealed to increase expressive levels of the tyrosine hydroxylase gene within the adrenal medullary cells, and influences the synthetic pathways of neurotrophic factors, nitric oxide synthase, and glutathione ***(Yakoob et al., 2016).***

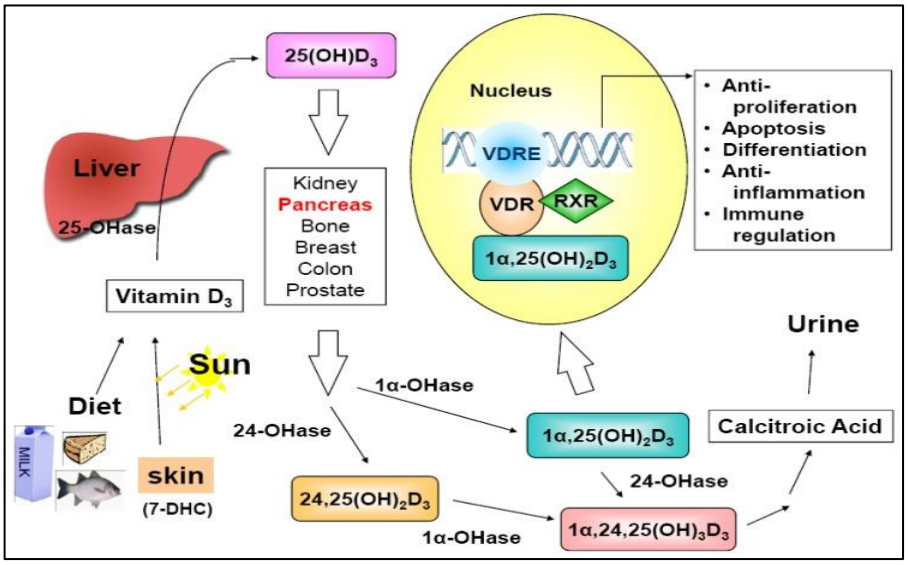

Figure (2): Metabolic pathways, synthesis and actions of vitamin D ***(Olmos et al., 2015).***

Vitamin D deficiency

A diet deficient in vitamin D in combination with insufficient sun exposure leads to pathological developmental process of osteomalacia (or rickets in children), which is described as softening of the bones. In the developed nations, this is a rare condition. On the other hand, researchers consider vitamin D deficiency have become a global issue within the elderly and is considered widespread in children and adults ***(Watkins et al., 2015; Elidrissy, 2016).***