Assessment of serum 25-hydroxy vitamin D in cirrhotic patients with and without spontaneous bacterial peritonitis

Thesis

For partial fulfillment of M.D. of Internal Medicine By

Ahmed Abd ElHakeem Mansour Amer
Master degree of internal medicine
Ain shams University

Under Supervision Of

Prof. Dr/ Sayed Mohammad Shalaby
Professor of Internal Medicine
Faculty of Medicine
Ain shams University

Prof. Dr/ Essam Mohammad Baiumy
Professor of Internal Medicine
Faculty of Medicine
Ain shams University

Prof. Dr/ Magdy Galal Eldin Abd Elrahman
Professor of Internal Medicine
Faculty of Medicine
Ain shams University

Prof. Dr/ Moataz Mohammed Sayed
Professor of Internal Medicine
Faculty of Medicine
Ain shams University

Dr/ Rania Mohamed Abdel halim
Lecture of clinical pathology
Faculty of Medicine
Ain shams University

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تقييم المصل ٢٥-هيدروكسي فيتامين D في مرضى التليف الكبدى مع وبدون التهاب الغشاء البريتونى الجرثومي العفوي

رسالة

توطئة للحصول على درجة الدكتوراة فى أمراض الباطنة العامة

مقدمة من

الطبيب/ أحمد عبد الحكيم منصور عامر
درجة ماجستير في الباطنة العامة جامعة عين شمس

تحت اشراف

الأستاذ الدكتور/ سيد محمد شلبي
أستاذ أمراض الباطنة العامة
كلية الطب-جامعة عين شمس

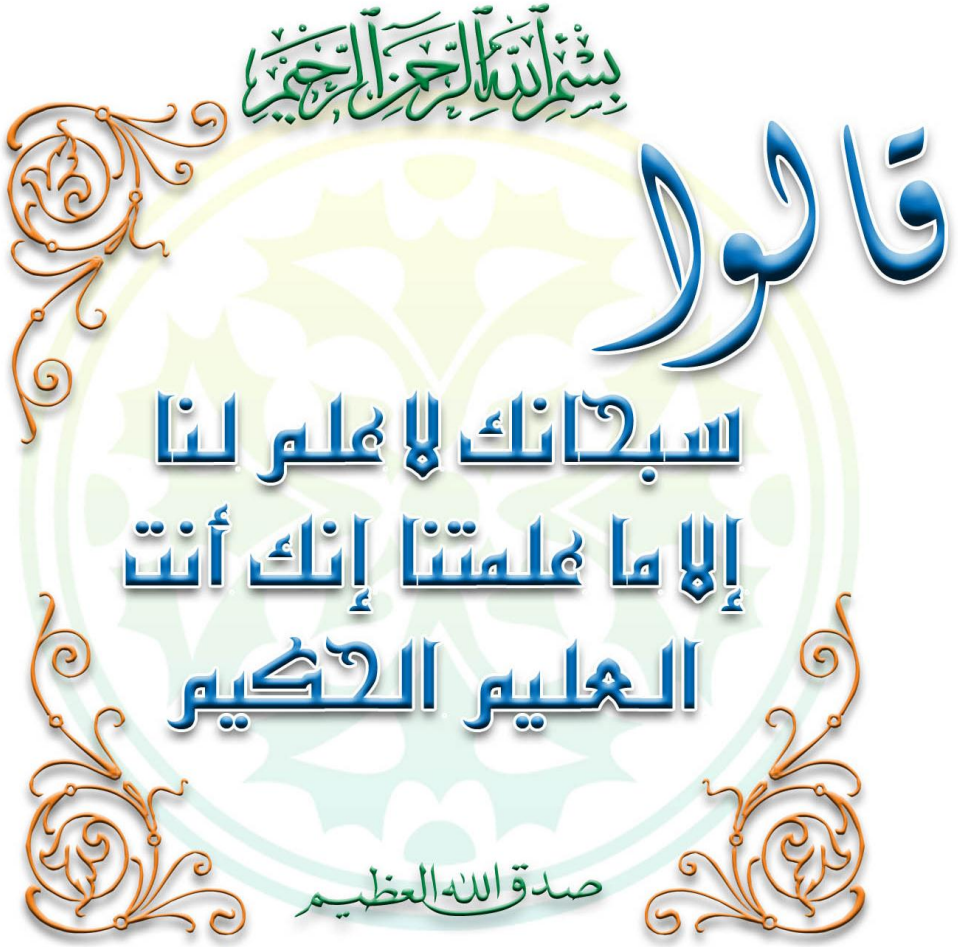
الأستاذ الدكتور/عصام محمد بيومى
أستاذ أمراض الباطنة العامة
كلية الطب جامعة عين شمس

الأستاذ الدكتور/ مجدى جلال الدين عبد الرحمن
أستاذ أمراض الباطنة العامة
كلية الطب جامعة عين شمس

الأستاذ الدكتور/ معتز محمد سيد
أستاذ أمراض الباطنة العامة
كلية الطب جامعة عين شمس

الدكتور/ رانيا محمد عبد الحليم
مدرس باثولوجيا اكلينيكية
كلية الطب جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١٩



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Ahmed Abdelhakeem Amer

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List of Abbreviations

Abb.	Full term

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

7-DHC ……... 7-dehydro- cholesterol

APRI…….. AST to Platelet Ratio Index

ACR……... acute cellular rejection

CD …….Crohn disease

CRP ……C-reactive protein

DBP ……vitamin D binding protein

ESCEO ……European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

HSCs……. ….Hepatic stellate cells

I-R ……..ischemic-reperfusion

KLF-4……. Krüppel-like factor

miRNAs ……... microRNAs

MPV …….mean platelet volume

NLR …….neutrophil-to-lymphocyte ratio

OR …….odds ratio

PDGF …….platelet-derived growth factor

Abb.	Full term

PSC …….. primary sclerosing cholangitis

PTH …….parathyroid hormone

RA …… rheumatoid arthritis

RCTs ……randomized controlled trials

RDA …….Recommended Dietary Allowance.

RXR ……...the retinoid X receptor

SBP…… Spontaneous bacterial peritonitis

PBC ……..…. primary biliary cirrhosis

SNP ……...Single Nucleotide Polymorphism

TH ……T helper cell

VDR …….... vitamin D receptor

Abstract

Background: Vitamin D has pleotropic effect including the immune function, it increases innate immunity and modifies lymphocyte activation. The risk for bacterial infections is increased in cirrhotic patients due to low levels of vitamin D, so its deficiency may be linked with the prevalence of SBP in cirrhotic patients

Aim: To assess the 25-OH vitamin D serum level in cirrhotic patients and it's relation to spontaneous bacterial peritonitis.

Methods: The current study included 90 patients divided into three groups; group one; patients with compensated liver cirrhosis, group two; patients with decompensated liver cirrhosis without SBP and group three; patients who had decompensated cirrhosis with SBP. The following laboratory work up was done: Serum 25-OH vitamin D level, liver functions test, kidney functions test, complete blood count, and ascitic neutrophil count.

Results: We report a highly significant difference between the studied groups as regards 25-OH vitamin D level, being lowest in group three. A negative correlation between markers of severe cirrhosis and vitamin D concentrations was found in our cirrhotic patients.

Conclusion: Vitamin D deficiency is associated with increased incidence of infections in cirrhotic patients including spontaneous bacterial peritonitis, suggesting that Vitamin D supplementation may be useful in these patients.

Keywords: Liver cirrhosis, vitamin D, and SBP.

INTRODUCTION

Vitamin D has pleiotropic functions. It is widely recognized to have a central role in calcium metabolism and bone mineralization. Vitamin D deficiency is causally related to rickets in children and osteomalacia in adults, but vitamin D is also physiologically important for the proper function of other organs such as skeletal muscle, heart, brain, and pancrease ***(Baeke et al., 2010).***

Vitamin D may also be implicated in innate and acquired immunity ***(Holick, 2007).***Vitamin D could increase innate defense and modulate the activation of lymphocytes implicated in the immune response, leading to a switch toward a T helper 2 response ***(Bikle, 2011).***

Vitamin D deficiency has been reported in the general population, even in sunny countries, although it is more frequent at high latitudes where seasonal variations in 25-OH (25-hydroxy) vitamin D have been described **(*Baeke et al., 2010).*** A low level of 25-OH vitamin D has been associated with increased mortality in the general population in observational studies ***(Zittermann et al., 2012).***

A low level of vitamin D in chronic liver disease patients can be attributed to multiple mechanisms, such as low sunlight exposure, malnutrition, intestinal edema complicating portal

hypertension leading to low intestinal absorption of vitamin D, or bile salt disruption caused by cholestasis. Another contributing factor, is the low levels of vitamin D-binding proteins (DBPs) and albumin, which transfer vitamin D to the liver and kidney for subsequent activation. Besides, low production of the active form of vitamin D caused by impaired hydroxylation by the liver ***(Stokes et al., 2013).***

Recently, a low 25-OH vitamin D level has also been reported to be associated with increased mortality in patients with alcoholic liver disease and in patients with cirrhosis, but the causal relationship is obscure. In a Belgian cohort of 324 patients, patients with a severe deficiency in 25-OH vitamin D (level below 10 ng/ml) had a significantly higher risk of death compared with those without a deficit ***(Trepo et al., 2013).***

As bacterial infections are frequent and are the cause of morbidity and mortality in patients with cirrhosis, many researchers hypothesized that the relationship between the lack of vitamin D and the increase in mortality observed in patients with cirrhosis could be because of an increase in bacterial infections ***(Putz-Bankuti et al., 2012).***

Spontaneous bacterial peritonitis (SBP), an infection of ascetic fluid without demonstrable intra-abdominal cause, is a complication of cirrhosis, with a reported mortality of 20% to 40% in adults ***(El-Shabrawi et al., 2011).***

AIM OF THE WORK

To assess the 25-OH vitamin D serum level in cirrhotic patients and it's relation to spontaneous bacterial peritonitis.

Chapter1
CLINICAL IMPLICATION OF VITAMIN D

Vitamin D deficiency has been recognized as a pandemic with a myriad of health consequences. Low vitamin D status has been associated with an increased risk of type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity, allergy, and even frailty ***(Holick, 2012).*** Low prenatal and neonatal vitamin D status may also increase susceptibility to schizophrenia, type 1 diabetes, and multiple sclerosis (MS) in later life via specific target organ effects, including the immune system, or through epigenetic modification ***(Lucas et al., 2008).***

Despite the many important health benefits of vitamin D, there is controversy regarding the definition of vitamin D deficiency and what the vitamin D requirement should be ***(Hossein-nezhad & Holick. 2012).***

Vitamin D metabolism and biological functions

Vitamin D (D represents D2, D3, or both) is a secosterol produced endogenously in the skin from sun exposure or obtained from foods that naturally contain vitamin D, including cod liver oil and fatty fish (eg, salmon, mackerel, and tuna); UV-irradiated mushrooms; foods fortified with vitamin D; and supplements ***(Hossein-nezhad & Holick. 2012).***

During exposure to sunlight, 7-dehydro- cholesterol (7-DHC) in the skin is converted to previtamin D3. The 7-DHC is present in all the layers of human skin. Approximately 65% of 7-DHC is found in the epidermis, and greater than 95% of the previtamin D3 that is produced is in the viable epidermis and therefore, cannot be removed from the skin when it is washed ***(Hossein-nezhad & Holick. 2013).***

Once previtamin D3 is synthesized in the skin, it can undergo either a photoconversion to lumisterol tachysterol, and 7-DHC or a heat-induced membrane-enhanced isomerization to vitamin D3. The cutaneous production of previtamin D3 is regulated. Solar photoproducts (tachysterol and lumisterol) inactive on calcium metabolism are produced at times of prolonged exposure to solar UV-B radiation, thus preventing sun- induced vitamin D intoxication. Vitamin D3 is also sensitive to solar irradiation and is, thereby, inactivated to suprasterol 1 and 2 and to 5,6-trans-vitamin D3 ***(Holick, 2007).***

Cutaneous vitamin D3 production is influenced by skin pigmentation, sunscreen use, time of day, season, latitude, altitude, and air pollution ***(Holick, 2012).***

An increase in the zenith angle of the sun during winter and early morning and late afternoon results in a longer path for the solar UV-B photons to travel through the ozone layer, which efficiently absorbs them. This is the explanation for why above and below approximately 33 latitude little if any vitamin D3 is made in the skin during winter. Because glass absorbs all