



EVALUATION OF VITAMIN D LEVEL IN TYPE 2 DIABETIC PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE

Thesis

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Presented by

Mohammed Hesham El-Ghannam

(M.B., B.Ch)

Supervised by

Prof. Dr. Salwa Seddik Hosny

Professor of Internal Medicine and Endocrinology

Faculty of Medicine, Ain Shams University

Dr. Hanan Mahmoud Ali

Lecturer of Internal Medicine and Endocrinology

Faculty of Medicine, Ain Shams University

Dr. Wesam Ahmed Mohammed

Lecturer of Internal Medicine and Endocrinology

Faculty of Medicine, Ain Shams University

**Faculty of Medicine
Ain Shams University**

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تقييم مستوى فيتامين د فى مرضى السكرى من النوع الثانى المصابين بدهن الكبد الغير كحولى

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مقدمة من

□ محمد هشام الغنام/الطبيب

بكالوريوس الطب و الجراحة

تحت إشراف

□ أ.د/ سلوى صديق حسنى

أستاذ الباطنة العامة و الغدد الصماء

كلية الطب- جامعة عين شمس

د/ حنان محمود على

مدرس الباطنة العامة و الغدد الصماء

كلية الطب- جامعة عين شمس

□ د/ وسام أحمد محمد

مدرس الباطنة العامة و الغدد الصماء

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لَسْبَحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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LIST OF ABBREVIATIONS

| | |
|--|--|
| 1,25(OH)₂D₃ | : 1 α ,25 dihydroxyvitamin D ₃ |
| 25(OH)D | : 25 hydroxyvitamin D |
| 2hpp | : 2 hour postprandial blood sugar |
| ALT | : Alanine aminotransferase |
| AMPK | : Adenosine monophosphate-activated protein kinase |
| APRI | : AST platelet ratio index score |
| AST | : Aspartate aminotransferase |
| BMI | : Body mass index |
| Ca⁺² | : Calcium |
| CAMP | : Cyclic adenosine monophosphate |
| CYP | : Cytochrome P450 |
| DDP4 | : Dipeptidyl peptidase 4 |
| DM | : Diabetes mellitus |
| ER | : Endoplasmic reticulum |
| FDA | : Food and drug administration |
| FIB-4 | : Fibrosis 4 |
| FLI | : Fatty liver index |
| FPG | : Fasting plasma glucose |
| FXR | : Farnesoid X receptor |
| GGT | : Gamma-glutamyl-transferase |
| GIP | : Glucose dependent insulintropic hormone. |
| GLP-1 | : Glucagon like peptide-1 |
| GLUT | : Glucose transporter |
| HbA1C | : Glycosylated hemoglobin |
| HDL | : High density lipoprotein |
| HLA | : Human leukocyte antigen |
| HSC | : Hepatic stellate cell |
| IBD | : Inflammatory bowel disease |
| IDF | : International diabetes federation |
| IFG | : Impaired fasting glucose |
| IGT | : Impaired glucose tolerance |
| IL | : Interleukin |
| INF-γ | : Interferon gamma |
| IR | : Insulin resistance |

List of Abbreviations

| | |
|--------------------------------|---|
| M-CSF | : Macrophage colony stimulating factor |
| MODY | : Maturity onset diabetes of the young |
| MRI | : Magnetic resonance imaging |
| MS | : Multiple sclerosis |
| NAFLD | : Non alcoholic fatty liver disease |
| NAS | : NAFLD activity score |
| NASH | : Non alcoholic steatohepatitis |
| NFS | : NAFLD fibrosis score |
| NF-κB | : Nuclear factor κ B |
| NPH | : Neutral protamine hagedron |
| NPL | : Neutral protamine lispro |
| OSA | : Obstructive sleep apnea |
| PAD | : Peripheral arterial disease |
| PCO | : Polycystic ovarian disease |
| PPAR gamma | : Peroxisome proliferator-activated receptor gamma |
| RA | : Rheumatoid arthritis |
| RANK | : Receptor activator of nuclear factor kappa-B |
| RANKL | : Receptor activator of nuclear factor kappa-B ligand |
| ROS | : Reactive oxygen species |
| RXR | : Retinoid X receptor |
| SAF | : Steatosis activity fibrosis score |
| SERCA | : Sacro/endoplasmic reticulum Ca^{+2} ATPase |
| SGLT 2 | : Sodium glucose co-transporter 2 |
| T1DM | : Type 1 diabetes mellitus |
| T2DM | : Type 2 diabetes mellitus |
| TG | : Triglyceride |
| TH1 | : Type 1 T helper cell |
| TLR | : Toll like receptor |
| TNFα | : Tumor necrosis factor alpha |
| VDR | : Vitamin D receptor |
| VLDL | : Very low density lipoprotein |
| WC | : Waist circumference |
| β cell | : Beta cell |

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Abstract

Background: Vitamin D has proven to have pleiotropic functions beside Calcium homeostasis as an immunomodulator and considerable effect on both insulin secretion and insulin sensitivity. Insulin resistance is a mutual pathological cause between type 2 diabetes mellitus (T2DM) and non alcoholic fatty liver disease.

The aim: The aim is to evaluate total vitamin D status in patients with T2DM(with diabetes duration more than five years) and NAFLD

Methods: 110 Egyptian subjects were conducted to this study after their written informed consent. They divided into 4 groups (30 patients with T2DM and NAFLD, 30 patients with diabetes only, 30 patients with NAFLD and 20 healthy controls). They subjected to full history, examination, laboratory investigation and abdominal ultrasound. Total vitamin D assessment is done using ELISA method. Causes of secondary steatosis and vitamin D deficiency are excluded. NAFLD was diagnosed by abdominal ultrasound and fatty liver index.

Results: Total Vitamin D is decreased in all patients groups compared to control (15.5 ± 7.4 , 24.4 ± 8.19 and 22.86 ± 9.58 vs 55.8 ± 11.98 ng/ml respectively) also it was lower in diabetic patients with NAFLD than either diabetic patients only or NAFLD only. (15.5 ± 7.46 vs 24.4 ± 8.19 and 22.86 ± 9.58 ng/ml respectively). Total vitamin D was negatively correlated with weight, body mass index, waist circumference, total cholesterol, LDL, triglycerides, fasting plasma glucose, glycosylated hemoglobin and fatty liver index

Conclusion: Total vitamin D level in diabetic patients with NAFLD is lower than either diabetic or NAFLD patients only. Also, it's lower in either diabetic or NAFLD patients than healthy

Key word: Vitamin D/ type 2 diabetes mellitus/ non alcoholic fatty liver disease

INTRODUCTION

Diabetes mellitus is a metabolic disorder that is characterized by disturbance of carbohydrate, protein and fat metabolism due to impaired insulin secretion, action or both (*Alberti and Zimmet, 1998*). The WHO estimates that diabetes resulted in 1.5 million deaths in 2012 making it the 8th leading cause of death (*WHO, 2016*).

It's also associated with multiple complication that affect micro and macro vascular including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes (*Michael, 2008*).

There's increasing evidence suggests that patients with type 2 diabetes are at a particularly high risk for developing the progressive forms of nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis and associated advanced liver fibrosis (*Prashanth et al., 2009*)

NAFLD is a pathological condition consisting of a spectrum of liver diseases due to macrovesicular accumulation of triglycerides within hepatocytes (hepatic steatosis). In developed countries, NAFLD is observed in 20-30% of the general population (*Browning et al., 2004*) and the prevalence of NAFLD may be present in up to 70% of patients with diabetes (*Williamson et al., 2011*). It

affects up to 25% Egyptian general population (*National liver institute, 2011*).

NAFLD is correlated with central obesity, insulin resistance, type 2 diabetes and may be another component of metabolic syndrome (*McCullough, 2004*)

NAFLD has been associated with increased risk of cardiovascular disease among type 2 diabetic patients independent of glycemic control (*Targher et al., 2005*). There's accumulating evidence suggests that altered vitamin D homeostasis is associated with NAFLD (*Scala et al., 2007*)

Vitamin D is a lipophilic molecule essential to calcium and phosphate balance and osteo-metabolic system regulation. It is produced onto the skin through a UV-mediated reaction, then it is metabolized to its active $1\alpha, 25$ (OH)₂ form through two consecutive hydroxylations exerted by kidney and liver, respectively (*Bruyère et al., 2007*)

Although the main function of vitamin D is to regulate bone metabolism, its deficiency has been related to many other organ systems (*Anderson et al., 2010*)

Vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, stroke and incident death. Vitamin D levels have been

additionally associated with obesity, inflammation and insulin resistance (*Chagas et al., 2012*)

Several studies have demonstrated that hypovitaminosis D has extra-skeletal effects that impact on the development of various pathologies including those that make up a large majority of morbidity and mortality; cancer, cardiovascular disease and diabetes also in development of NAFLD (*Richard et al., 2015*).

AIM OF THE WORK

The aim is to Assess Total vitamin D status in type 2 diabetic patients with non alcoholic fatty liver disease.