Evaluation of vitamin D level in type 2 diabetic patients with non alcoholic fatty liver disease

Thesis

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

رسالة

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List of Abbreviations

$1,25(OH)_2D3$	: 1α,25 dihydroxyvitamin D3
25(OH)D	: 25 hydroxyvitamin D
2hpp	: 2 hour postprandial blood sugar
ALT	: Alanine aminotransferase
AMPK	: Adenosine monophosphase-activated protein kinase
APRI	: AST platelet ratio index score
AST	: Aspartate aminotransferase
BMI	: Body mass index
Ca^{+2}	: Calcium
CAMP	: Cyclic adenosine monophosphase
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 insulinotropic 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

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-κβ	: Nuclear factor κβ
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

Backgroun: 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 NALFD 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.