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VITAMIN D STATUS IN NON-ALCOHOLIC FATTY LIVER DISEASE

By

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ABSTRACT

Background: Hypovitaminosis D has been recognized as a worldwide epidemic. Since vitamin D exerts significant metabolic activities comprising free fatty acids (FFA) flux regulation from the periphery to the liver, its deficiency may promote fat deposition into the hepatocytes.

Objective: To investigate plasma vitamin D levels in non-alcoholic fatty liver disease patients.

Patients and methods: This prospective study was carried out at Al-Hussein Hospital, Faculty of Medicine, Al- Azhar University, from June 2019 till December 2019. The present study included 40 middle aged patients which were divided into 2 equal groups: Patients with NAFLD, and patients with NASH who presented with elevated liver enzymes and newly diagnosed via abdominal Ultrasonography or computed tomography (CT). In addition, 20 apparently healthy subjects with normal weight and normal level of vitamin D were included as control group.

Results: There was a high significant positive correlation between serum vit. D3 and age, between serum vit D3 and serum albumin. There was a significant positive correlation between Serum VIT D3 and serum urea. Also, there was a high significant negative correlation between serum VIT D3 and ALT, AST, serum bilirubin, direct and 2hpp blood sugar, BMI and Hip circumference.

Conclusion: Lower serum 25(OH)D levels were found in NAFLD patients than in subjects without NAFLD.

Keywords: Vitamin D, Non-alcoholic Fatty Liver Disease, Hepatosteatosis, Prospective.

INTRODUCTION

Vitamin D has a significant role in many crucial physiological processes, including insulin resistance, muscle contraction, immune function, and calcium and bone metabolism. The prevalence of vitamin D deficiency ranges from 52 to 72% of the patients as indicated by several National Health Nutrition Surveys involving different countries *(Szymczak-Pajor and Śliwińska, 2019).*

The role of serum vitamin D was emphasized in chronic liver diseases and non-alcoholic fatty liver disease (NAFLD) in particular. For instance, a population-based cohort study, consisting of 1081 participants, suggested that low serum vitamin D is closely related to NAFLD in patients with insulin resistance and diabetes, independent of abdominal visceral fat *(Seo et al., 2013).*

Another study compared 607 NAFLD patients with matched controls and found

that low serum vitamin D concentrations were associated with NAFLD, and might have a role in the development and progression of NAFLD *(Jablonski et al., 2013).*

Dasarathy et al. (2013) evaluated 148 biopsy-proven NAFLD patients and found that serum vitamin D was negatively correlated not only with hepatic steatosis and inflammation, but also with visceral and abdominal fat.

Furthermore, a case control study showed that NAFLD patients had low serum vitamin D due to inadequate vitamin D and calcium intake *(Hashemi et al., 2013).* Meta-analysis of 17 cross sectional studies also showed that serum 25-hydroxy vitamin D (25OHD) level had an association with fatty liver diseases *(Eliades et al., 2013).*

Moreover, a study assessing the amount of liver fat by proton magnetic resonance spectroscopy (1H-MRS) showed that plasma 25OHD levels were not associated with insulin resistance and intrahepatic fat accumulation. Although there are several studies clearly indicating decreased serum vitamin D in patients with NAFLD, the mechanism is poorly understood *(Seung et al., 2017).*

Serum vitamin D is either synthesized by ultraviolet (UV) rays in the skin or taken orally. Vitamin D3 (cholecalciferol) in blood is transformed into 25-hydroxy vitamin D via the liver. It remains unclear whether the low vitamin D concentration associated with NAFLD is the result of decreased dietary intake, decreased sun exposure, or decreased conversion of 25(OH)D because of parenchymal liver disease. Since NAFLD is a consequence of nutritional over-intake, it remains highly controversial whether or not vitamin D intake is reduced in NAFLD patients *(Han et al., 2014).*

There is a lack of international research validating the routine screening of vitamin D deficiency and the effects of supplementation. Moreover, there is no evidence suggesting that NAFLD patients experience less sun exposure compared with non-NAFLD obese patients *(Seung et al., 2017).*

The present study aimed to investigate plasma vitamin D levels in NAFLD patients.

PATIENTS AND METHODS

The present study included 40 middle aged patients which were divided into 2 equal groups: Patients with NAFLD, and patients with NASH who presented with elevated liver enzymes and newly diagnosed via abdominal Ultrasonography or computed tomography (CT). In addition, 20 apparently healthy subjects with normal weight and normal level of vitamin D were included as control group. This prospective study was carried out at Al-Hussein Hospital, Faculty of Medicine, Al- Azhar University, from June 2019 till December 2019.

Exclusion criteria: Alcohol consumption, patients who took medications known to induce fatty liver, serum creatinine>1.5 mg/dl or chronic renal disease, patients with hepatitis B or hepatitis C, patients who received medication to control blood glucose, blood pressure, or lipid lowering agent, central obesity (waist circumference > 80 cm in women, >90 cm in men), abnormal blood pressure (systolic > 130 mmHg or diastolic > 85 mmHg), abnormal triglycerides (>150 mg/dl), low

HDL cholesterol (<50 mg/dl) and abnormal fasting glucose (>100 mg/dl).

Clinical assessment: Complete history taking, clinical examination: BMI and waist and hip circumference and anthropometric measurements.

Laboratory assessment (routine and general evaluation tests):

Complete blood count, liver function tests (serum bilirubin "total, direct and indirect", ALT, AST, total proteins and serum albumin), serum levels of 25-Hydroxy vitamin D ng/ml: Serum is separated and stored in -25℃ for few days. 25(OH) vitamin D levels were measured using The Alegria® 25-OH Vitamin D3/D2 Test Strip (ORGENTEC Diagnostika GmbH Carl-Zeiss-Straβe 49-51 Mainz – Germany). It is an ELISA based test.

Radiological assessment: Abdominal ultrasonography (US), Abdominal Contrast-enhanced computed tomography (CT) scan in HCC patients.

Statistical analysis:

Analysis of data was done using Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of range, mean and standard deviation. Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student's t-test was performed. Qualitative variables were compared using chi-square (X2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed. A P value < 0.05 was considered significant.

RESULTS

There were significant differences between the studied groups as regard age, ALT, AST, serum bilirubin direct, serum bilirubin total, serum albumin, serum urea, serum create, F.B. sugar, 2hpp, serum cholesterol, serum T.G, HDL, LDL, serum VIT D3, SBP, DBP, BMI, waist

circumference and hip circumference **(Table 1)**.

Table (1): Comparison between the three groups regarding the studied parameters

Parameters \ Groups		Patients with NAFLD N=20			Patients with NASH N=20			Control N=20			ANOVA	TUKEY'S Test		
											P-value	I&II	I&III	II&III
Age (Years)	**Range**	39	-	44	35	-	40	34	-	40	<0.001	<0.001	<0.001	0.193
	Mean ±SD	41.55	±	1.395	38.5	±	1.318	37.7	±	1.593				
ALT (U/L)	**Range**	48	-	60	70	-	90	25	-	38	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	53.3	±	3.114	80.35	±	5.641	29.85	±	4.133				
AST (U/L)	**Range**	50	-	70	75	-	95	20	-	37	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	56	±	5.758	84.85	±	6.002	32.25	±	4.598				
Serum Bilirubin Direct (mg/dl)	**Range**	0.25	-	0.39	0.37	-	0.44	0.2	-	0.27	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	0.32	±	0.04	0.397	±	0.019	0.229	±	0.028				
Serum Bilirubin Total (mg/dl)	**Range**	1	-	1.3	1.1	-	1.5	0.8	-	1.1	<0.001	0.021	<0.001	<0.001
	Mean ±SD	1.17	±	0.108	1.26	±	0.119	0.975	±	0.079				
Serum Albumin (g/dl)	**Range**	3.5	-	4.5	3	-	4.1	3.9	-	5	<0.001	0.020	<0.001	<0.001
	Mean ±SD	3.965	±	0.272	3.695	±	0.265	4.62	±	0.375				
Serum Urea (mg)	**Range**	20	-	37	20	-	28	15	-	25	<0.001	<0.001	<0.001	0.094
	Mean ±SD	29	±	5.292	23.4	±	2.604	20.9	±	2.594				
Serum Create (mg/dl)	**Range**	0.8	-	1.1	0.8	-	1.1	0.6	-	0.9	<0.001	0.114	0.002	<0.001
	Mean ±SD	0.923	±	0.092	0.98	±	0.101	0.823	±	0.073				
F.B. Sugar (mg/dl)	**Range**	90	-	109	85	-	105	85	-	100	<0.001	0.004	<0.001	0.001
	Mean ±SD	101.95	±	5.042	96.3	±	6.586	89.85	±	4.158				
2hpp (mg/dl)	**Range**	100	-	120	105	-	135	80	-	110	<0.001	0.001	<0.001	<0.001
	Mean ±SD	110.75	±	6.742	120.2	±	7.824	97.65	±	8.171				
Serum Cholesterol (mg/dl)	**Range**	110	-	150	170	-	185	95	-	130	<0.001	<0.001	0.043	<0.001
	Mean ±SD	132	±	11.286	163.6	±	36.574	114.25	±	9.072				
Serum T.G (mg/dl)	**Range**	125	-	145	129	-	148	89	-	110	<0.001	0.091	<0.001	<0.001
	Mean ±SD	135.85	±	6.268	139.85	±	5.184	99.1	±	6.215				
HDL (mg/dl)	**Range**	40	-	60	45	-	65	40	-	55	<0.001	0.002	0.034	<0.001
	Mean ±SD	51.75	±	5.684	58	±	5.712	47.25	±	5.22				
LDL (mg/dl)	**Range**	70	-	90	80	-	98	50	-	68	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	80.45	±	5.083	89.25	±	5.035	60.15	±	5.153				
Serum VIT D3 (ng/ml)	**Range**	11	-	17	8	-	13	35	-	50	<0.001	0.001	<0.001	<0.001
	Mean ±SD	14.65	±	1.565	10.8	±	1.361	42.3	±	5.212				
SBP	**Range**	100	-	115	105	-	125	95	-	110	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	108.25	±	4.94	116	±	7.182	100.25	±	5.495				
DBP	**Range**	60	-	75	60	-	85	60	-	80	0.036	0.038	0.857	0.124
	Mean ±SD	68	±	4.974	72.75	±	7.34	69	±	5.282				
BMI	**Range**	19	-	22	20	-	24	17	-	22	<0.001	<0.001	0.042	<0.001
	Mean ±SD	20.6	±	1.142	22.4	±	1.095	19.6	±	1.536				
Waist circumference (cm)	**Range**	70	-	80	72	-	81	67	-	77	<0.001	0.03	0.008	<0.001
	Mean ±SD	73.85	±	2.925	76.1	±	2.469	71.15	±	2.758				
Hip circumference (cm)	**Range**	87	-	94	90	-	98	80	-	88	<0.001	<0.001	<0.001	<0.001
	Mean ±SD	90.65	±	1.954	94.45	±	2.139	84.65	±	2.084				

There were high significant positive correlations between Serum VIT D3 and age and between Serum VIT D3 serum albumin, there is significant positive correlation between Serum VIT D3 and serum urea, also there is high significant negative correlation between Serum VIT D3 and ALT, AST, Serum Bilirubin Direct, 2hpp, BMI and Hip circumference, there is significant negative correlation between Serum VIT D3 and Serum Bilirubin Total, Serum Cholesterol, HDL,

LDL, SBP, DBP and Hip circumference, but there is no significant correlation between Serum VIT D3 and F.B. Sugar or Serum T.G **(Table 2)**.

Table (2): Correlation between Vit D and other studied parameters

Groups / Parameters	Patients with NAFLD		Patients with NASH		Total	
	r	P-value	r	P-value	r	P-value
Age (Years)	0.069	0.773	0.000	1.000	0.621	<0.001
ALT (U/L)	-0.129	0.589	-0.175	0.459	-0.790	<0.001
AST (U/L)	-0.397	0.083	0.028	0.906	-0.789	<0.001
Serum Bilirubin Direct (mg/dl)	-0.163	0.492	-0.229	0.332	-0.694	<0.001
Serum Bilirubin Total (mg/dl)	0.059	0.805	-0.085	0.723	-0.308	0.043
Serum Albumin (g/dl)	0.353	0.127	0.070	0.769	0.486	0.001
Serum Urea (mg)	-0.222	0.346	-0.214	0.365	0.351	0.026
Serum Create (mg/dl)	-0.379	0.099	-0.146	0.539	-0.385	0.014
F.B. Sugar (mg/dl)	-0.196	0.408	-0.263	0.263	0.234	0.145
2hpp (mg/dl)	-0.273	0.244	-0.213	0.366	-0.564	<0.001
Serum Cholesterol (mg/dl)	-0.405	0.076	0.432	0.057	-0.320	0.044
Serum T.G (mg/dl)	-0.016	0.945	-0.154	0.518	-0.311	0.051
HDL (mg/dl)	-0.075	0.752	0.047	0.843	-0.403	0.010
LDL (mg/dl)	0.100	0.674	0.200	0.399	-0.470	0.002
SBP	0.257	0.274	-0.194	0.413	-0.433	0.005
DBP	0.243	0.301	-0.522	0.018	-0.391	0.013
BMI	-0.230	0.330	-0.120	0.614	-0.593	<0.001
Waist circumference (cm)	-0.449	0.047	0.147	0.536	-0.423	0.007
Hip circumference (cm)	0.078	0.743	0.014	0.952	-0.533	<0.001

DISCUSSION

The exact mechanism of NAFLD development is unknown. However, NAFLD has the potentiality of progression to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC). It is commonly associated with insulin resistance and metabolic syndrome *(Younossi et al., 2018).*

Vitamin D has many functions in many systems of the human body including muscles, bone, heart, gut, liver and immune system *(Vernetti et al., 2017).* Vitamin D may have a role in development of autoimmune diseases and inflammatory conditions through production of inflammatory cytokines *(Alhassan et al., 2017).*

Some studies found a significant association between vitamin D deficiency and obesity, metabolic syndrome, type 2 diabetes and insulin resistance *(Zaki et al., 2017).* Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disease in adolescents and its prevalence has risen substantially in recent decades *(Cho et al., 2019).*

Several different parallel processes participate in the development of NAFLD *(Adams et al., 2017)* and many potential risk factors for NAFLD, including obesity, insulin resistance, and metabolic syndrome, have been identified. Vitamin D deficiency has been investigated as a risk factor for the development of NAFLD and several studies have suggested that vitamin D levels were inversely associated with NAFLD in adults *(Cimini et al.,*

2019). However, few studies have investigated the relationship between vitamin D deficiency and NAFLD in an adolescent population *(Cho et al., 2019)*.

Vitamin D status has traditionally been considered an important factor in calcium-associated metabolism. In addition, recent attention has focused on the extra-skeletal effects of vitamin D *(Cho et al., 2019)* and increasing evidence has shown that low serum vitamin D levels were associated with obesity and metabolic syndrome *(Mahmood et al., 2017)*.

Shawky et al. (2018) conducted a cross sectional study in Egypt performed to investigate the association between NAFLD and serum 25(OH) vitamin D, they enrolled 50 patients with NAFLD cases.

In the present study, serum levels of Vit D. were significantly lower in patients than controls and in NASH patients than patients with NEFLD. This was in agreement with *Shawky et al. (2018)* who reported that Serum 25(OH) vitamin D levels were significantly reduced in patients with NAFLD than those without NAFLD (18.76 vs 40.36 p value 0.000). Serum 25(OH) vitamin D levels decreased with the increase in the NAFLD grade. However, no significant difference in serum 25(OH) vitamin D level between patients with grade 1 NAFLD and those without NAFLD, but there were significant differences between patients with grade 2 and 3 on one hand and those with grade 1 and 0 on the other hand.

In the present study, serum levels of ALT, AST, Serum Bilirubin Direct, Serum total Bilirubin, Serum Albumin, Serum urea, Serum create, Serum FBS, 2hpp, Serum Cholesterol, Serum TG, Serum HDL and Serum LDL were significantly higher in patients than controls and in NASH patients than those with NEFLD. *Shawky et al. (2018)* verified that patients with NAFLD showed higher white blood cell count, fasting blood sugar (FBS), ALT, triglycerides and total cholesterol levels than controls. Also, *Cho et al. (2019)* noticed in their study that glucose, cholesterol, and TG levels were higher in adolescents with suspected NAFLD than in adolescents without suspected NAFLD.

Küçükazman et al. (2014) found that NAFLD and control groups did not differ in terms of gender or age. Also, they illustrated that the NAFLD group had significantly higher fasting blood glucose (FBG), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-glutamyltransferase (GGT), alkaline phosphatase (ALP), HbA1c, ferritin, insulin, C-peptide, HOMA-IR, total cholesterol, triglyceride (TG) and white blood cell (WBC) levels. In contrast, the NAFLD group had significantly lower 25OHD levels compared with those of the control group.

Fogelstrand and Boren (2012) investigated the role of 25(OH)D in NAFLD patients and matched the NAFLD group with a presumably healthy population that did not undergo liver US. They found a strong inverse relationship between NAFLD and 25(OH)D levels. Also, *Barchetta et al. (2011)* found strong association between hypovitaminosis D and NAFLD which was independent on age, sex, BMI, lipid profile or glucose level.

Rhee et al. (2013) found a minor but significant difference in 25(OH)D levels between patients with and without NAFLD. However, *Park et al. (2017)* showed that vitamin D deficiency was significantly related to NAFLD in men but not in women. *Cho et al. (2019)* stated that adolescents with suspected NAFLD had significantly lower 25(OH)D levels than adolescents without suspected NAFLD.

Chung et al. (2016), Nelson et al. (2016) and *Zhai et al. (2016)* found that low levels of vitamin D are associated with high risk of NASH in patients with NAFLD and vitamin D deficient patients have 1.26-fold increased risk for NAFLD than those with sufficient vitamin D.

In contrast to our results, *Liangpunsakul and Chalasani (2011)* conducted adult population-based studies in which they have noted that low vitamin D levels were independently related to NAFLD. Also, our results were in contrary with *Patel et al. (2016)* and *De Paula et al. (2017)* who found no significant differences between patients with NAFLD and those without NAFLD in serum vitamin D levels.

In another study by *Katz et al. (2011),* low vitamin D levels were not found to be an independent predictor of suspected NAFLD in 1,630 adolescents after adjusting for obesity. These contradictory results among studies may be related to differences in the studied population, nutritional and environmental factors. *Nobili et al. (2014)* showed that low vitamin D levels were independently associated with liver biopsy-proven NAFLD in adolescents.

Nair (2010) stated that the mechanisms by which 25(OH) vitamin D may induce NAFLD is not clear. The liver converts vitamin D to its active form, 25 (OH) vitamin D, so in liver diseases the 25 (OH) vitamin D level. *Eliades and Spyrou (2015)* found that vitamin D deficiency may induce NAFLD by impairing hepatic lipid metabolism.

Alvarez and Ashraf (2010) demonstrated that Patients with vitamin D deficiency found to have high rates of insulin resistance, metabolic syndrome and inflammatory mediators including IL-4, IL-6 and TNF-α. *Barchetta et al. (2012)* reported that vitamin D receptors widely exist in liver tissue with negative association between vitamin D receptors expression and necro-inflammatory grades of NASH. However, *Earthman et al. (2012)* stated that Vitamin D may be sequestrated in the adipose tissue in obese patients.

In the present work, we found that there was a significant positive correlation between Serum VIT D3 and age and between Serum VIT D3 serum albumin. There was a significant positive correlation between Serum VIT D3 and serum urea. Also, there were significant negative correlations between Serum VIT D3 and ALT, AST, Serum Bilirubin Direct, 2hpp, BMI and Hip circumference. There were significant negative correlations between Serum VIT D3 and Serum Bilirubin Total, Serum Cholesterol, HDL, LDL, SBP, DBP and Hip circumference, but there were no significant correlations between serum vit D3 and FBS or Serum T.G.

This was in concordant with *Shawky et al. (2018)* who showed that serum 25(OH)

vitamin D levels were found to be correlated with age, BMI, ALT, AST, triglycerides, LDL and total cholesterol. *Küçükazman et al. (2014)* stated that the levels of 25(OH)D were significantly correlated with BMI, HbA1c levels, the urinary albumin/creatinine ratio, FBG levels, the erythrocyte sedimentation rate (ESR), uric acid levels, total cholesterol levels, LDL-C levels and HDL-C levels.

CONCLUSION

Serum 25OHD levels were lower in NAFLD patients than in subjects without NAFLD. This finding may have been related to low UV light exposure in the winter months or to genetic differences between different cultures.

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حالة فيتامين (د) فى مرض الكبد الدهني غير الكحولي

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خلفيـــة البحـــث: يعتبـــر نقـــص فيتـــامين د وبـــاءاً عالميـــاً. ونظـــراً لأن فيتـــامين د يمـــارس أنشـــطة أيضـــية تشـــتمل علـــى تنظـــيم تـــدفق الأحمـــاض الدهنيـــة الحـــرة مـــن الاطـــراف إلـــى الكبـــد، لـــذا فـــإن نقص فيتامين د قد يعزز ترسب الدهون في خلايا الكبد.

الهـــدف مـــن البحـــث: فحـــص مســـتويات فيتـــامين (د) فـــي البلازمـــا لـــدى مرضـــى أمـــراض الكبـــد الدهني غير الكحولي.

المرضـــى وطـــرق البحـــث: أجريـــت هـــذه الدراســـة فـــي مستشـــفى الحســـين، كليـــة الطـــب، جامعـــة الأزهـــر، مـــن يونيـــو 2019 حتـــى ديســـمبر 2019 وهـــي دراســـة مســـتقبلية شـــملت 40 شخصًـــا فـــي منتصـــف العمـــر مقســـمين إلـــى مجمـــوعتين متســـاويتين: مجموعـــة مصـــابون بمـــرض الكبـــد الـــدهني غيـــر الكحـــولي ومجموعـــة مصـــابون بالتهـــاب الكبـــد الـــدهني غيـــر الكحـــولي هـــذا بالإضـــافة إلـــى 20 شخصًـــا يبـــدون متمعتـــين بصـــحة جيـــدة كمجموعـــة تحكـــم. وتـــم قيـــاس مســـتوي فيتـــامين د فـــي المرضـــي المصـــابون بمـــرض الكبـــد الـــدهني غيـــر الكحـــولي كمـــا تـــم قياس فيتامين د في مجموعة التحكم.

نتـــائج البحـــث: كانـــت هنـــاك علاقـــة ارتبـــاط موجبـــة بـــين مســـتوى فيتـــامين د3 والعمـــر. وبـــين مســـتوى الألبـــومين و فيتـــامين د3 فـــي الـــدم. كمـــا كانـــت هنـــاك علاقـــة إرتبـــاط موجبـــة بـــين مســـتوى فيتـــامين د3 و اليوريـــا فـــي الـــدم أيضًـــا، لكـــن كـــان هنـــاك علاقـــة ارتبـــاط ســـلبي كبيـــر بـــين مســـتوى فيتـــامين د3، ALT، AST، البيليـــروبين المباشـــر و مســـتوى الســـكر بالـــدم بعـــد الوجبة بساعتين، مؤشر كتلة الجسم ومحيط الورك.

الاســـتنتاج: مســـتويات فيتـــامين د3 منخفضـــة فـــي مرضـــى الكبـــد الـــدهني غيـــر الكحـــولي عنهـــا في الأشخاص الغير مصابين بمرض الكبد الدهني غير الكحولي.

الكلمات الدالة: فيتامين د، مرض الكبد الدهني غير الكحولي، تنكس الكبد، إستباقية.