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Efficiency of Treatment with Vitamin D on Biochemical Indexes, Lipid Profile, and Fatty Liver Indexes in Type 2 Diabetic Patients with Vitamin D Deficiency and Nonalcoholic Fatty Liver

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ABSTRACT

Prevalence of metabolic syndrome, type 2 diabetes, and non alcoholic fatty liver has been recently on rise in worldwide. This study was conducted to explore the association between vitamin D deficiency and incidence of fatty liver disease in type 2 diabetes patients and also to examine the efficacy of treatment with vitamin D in type 2 diabetes patients with vitamin D deficiency and non alcoholic fatty liver referring a specialty clinic in Shahrekord. In the first step (cross-sectional phase) of this two-step study, 108 patients with type 2 diabetes were examined for vitamin D level, biochemical indexes, lipid profile, and fatty liver indexes. In the second step (clinical trial phase), individuals with nonalcoholic fatty liver and vitamin D deficiency as treatment group underwent treatment with 50000 vitamin D units a week for 12 weeks. 3.96% of patients had fatty liver and 1.61% of patients had vitamin D deficiency of different severities. There was no significant association found between vitamin D deficiency and presence or severity of nonalcoholic fatty liver in patients ($P>0.05$). Treatment with vitamin D had no significant effect on biochemical indices, liver function, fasting blood sugar, and hemoglobin A1c ($P>0.05$), but serum level of cholesterol and low density lipoprotein (LDL) decreased in treatment patients compared to control group ($P<0.001$). No significant association was found between vitamin D deficiency and presence or severity of nonalcoholic fatty liver; but treatment of type 2 diabetes patients with vitamin D supplementation decreased the serum level of cholesterol and LDL.

Keywords: Fatty Liver, Type 2 Diabetes, Vitamin D, Cholesterol, Low density lipoprotein.

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INTRODUCTION

Today diabetes is a global challenge [1, 2]. Diabetes is related to a lot of dysfunctions in different organs of the body [3-6]. Insulin resistance as an introduction to diabetes is the basis for development of metabolic syndrome and even before the onset of overt diabetes could have adverse effects on liver cells. Recent studies have indicated that fatty liver disease increase in severity as the number of diseases causing metabolic syndrome; in other words, fatty liver is the hepatic manifestation of metabolic syndrome [7]. In fact, non alcoholic fatty liver is a complication of diabetes. Fatty liver disease includes a range of mild liver diseases as fat accumulation in liver cells which may lead to liver cell inflammation and then, through destroying liver cells, an irreversible chronic disease called cirrhosis throughout their course in a subset of patients [8]. Some studies have also demonstrated association of non alcoholic fatty liver with metabolic syndrome and type 2 diabetes [9-13].

Nowadays vitamin D deficiency is considered a global epidemic [14, 15]. The studies conducted in the USA, Europe, India, and East Asia have indicated that over 50% of children and adults are at high risk of vitamin D deficiency [16]. Moreover, the association of vitamin D deficiency with diabetes, cardiovascular diseases, kidney disorders, and non alcoholic fatty liver has been reported [17-20]. Vitamin D is able to exert favorable effects on both peripheral tissues and hepatocytes through decreasing fatty acids-induced insulin resistance [21]. Therefore it is argued that the level of vitamin D predisposes one to fat accumulation in liver and finally non alcoholic fatty liver. A meta analysis in 2013 also indicated that the patients with non alcoholic fatty liver had lower vitamin D serum levels than healthy individuals [22]. However in a study of some Chinese subpopulations no association between vitamin D deficiency and non alcoholic fatty liver was reported [23].

Since the prevalence of metabolic syndrome, type 2 diabetes, and non alcoholic fatty liver has been recently on rise in Iran and worldwide and given very high prevalence of vitamin D deficiency and inconsistent findings on the association between vitamin D deficiency and non alcoholic fatty liver, and also the necessity of prevention and treatment of non alcoholic fatty liver, type 2 diabetes control, and reduction in the complications due to non alcoholic fatty liver, this study was conducted to explore the association between vitamin D deficiency and incidence of fatty liver disease in type 2 diabetes patients and also to examine the efficacy of treatment with vitamin D in type 2 diabetes patients with vitamin D deficiency and non alcoholic fatty liver referring a specialty clinic in Shahrekord.

MATERIALS AND METHODS

This study was conducted in two phases. In the first phase which was conducted as a cross-sectional study to investigate the association between vitamin D deficiency and incidence and severity of fatty liver disease in the patients with type 2 diabetes, all diabetes patients referring Imam Ali Specialty Clinic of Shahrekord comprised the study population. The inclusion criteria into the study were at least six months passing since definite diagnosis of diabetes and being on treatment. The patients with history of alcohol abuse, hepatitis B or C, clinical symptoms of chronic liver failure, and renal failure, on medications causing fatty liver, with pregnancy and breastfeeding, and also history of thyroid diseases were excluded from the study. Overall 108 patients with type 2 diabetes referring the clinic under study were enrolled per convenience sampling. The data of all the patients were gathered by a researcher-developed checklist after consent to participate in the study was obtained from them. Demographic characteristics and anthropometric indices (height, weight, waist circumference, hip circumference, and body mass index [BMI]) of the patients were also recorded. Serum samples were obtained from fasting patients to examine the levels of fasting blood sugar (FBS), hemoglobin A1c, total cholesterol, high density lipoprotein (HDL), triglyceride, and 25(OH)D. All the patients were examined for the levels of vitamin D, biochemical indices, lipid profile, and fatty liver indices. Metabolic syndrome was diagnosed by NCEP ATP-III criteria [24]. The severity of fatty liver disease was determined by ultrasound (Siemens G50). Normal levels of vitamin D were determined by the latest guideline of American Association of Clinical Endocrinologists and incidence and severity of fatty liver disease were defined per Saverymuttu criteria [25]. For vitamin D, 100-300 ng/mL was considered as normal, 20-30 ng/mL as mild vitamin D deficiency, 10-20 ng/mL as moderate vitamin D deficiency, and less than 10 ng/mL as severe vitamin D deficiency. Fatty liver disease was diagnosed by complete ultrasound performed by a radiologist blind to the results of laboratory tests and classified into four degrees: degree 0 (no fatty liver), degree 1 (mild fatty liver), degree 2 (moderate fatty liver), and degree 3 (severe fatty liver).

In the second phase of the study which was conducted as a clinical trial, type 2 diabetes patients with non alcoholic fatty liver and vitamin D deficiency (n: 65) were assigned to treatment group and underwent treatment with 50000 vitamin D units a week for 12 weeks. Of these patients four were excluded because of not adhering to treatment protocol. The patients with fatty liver and no vitamin D deficiency (n: 42) were assigned to control group. At completion of the treatment, vitamin D level, biochemical indices, lipid profile, fatty liver indices, and fatty liver severity were measured and compared between the two groups.

Statistical assessment

The data were analyzed by descriptive and analytical (chi-square, paired and independent t-test, and correlation test) in SPSS 16.

RESULTS AND DISCUSSION

Of 108 studied patients, 69 (63.9%) patients were female. For the type of treatment, 74 (68.5%) were under treatment with oral diabetes medications, 31 (28.7%) with insulin, and three (2.8%) with hypoglycemic and insulin-lowering drugs. Mean duration of diabetes was derived 7.78±5.52 years.

Of all the patients, only four (3.7%) patients did not have fatty liver disease and the rest had fatty liver at different degrees. The most prevalent degree of fatty liver was degree 2. No significant difference was seen in the prevalence of different degrees of fatty liver between men and women (P=0.69) (Table 1).

Table 1. Severity of fatty liver disease in the patients under study

Fatty liver degree	Women		Men		All patients	
	No.	%	No.	%	No.	%
Degree 0	2	1.85	2	1.85	4	3.70
Degree 1	26	24	18	16.70	44	40.70
Degree 2	38	35.16	17	15.74	55	50.90
Degree 3	3	2.75	2	1.85	5	4.60
Total	69	63.89	39	36.11	108	100

Mean level of vitamin D in all type 2 diabetes patients under study was 76.6±38.42 nMol/L. Also mean vitamin D level was 69.92±27.2 nMol/L in men and 7.78±5.52 nMol/L in women with no significant difference (P=0.46) (Table 2).

Table 2. Status of vitamin D deficiency in all the patients under study

Vitamin D status	Women		Men		All patients	
	No.	%	No.	%	No.	%
Normal	29	26.87	13	12.03	42	38.90
Mild deficiency	23	22.31	19	17.59	42	38.90
Moderate deficiency	14	12.94	6	5.56	20	18.50
Severe deficiency	3	2.77	1	0.93	4	3.70
Total	69	63.89	39	36.11	108	100

Vitamin D deficiency was not significantly associated with duration of diabetes, age, gender, abdominal obesity, BMI, waist circumference, hip circumference, and blood pressure in the studied patients (P>0.05). Further no significant association was seen between vitamin D deficiency and metabolic syndrome in the patients (P>0.05).

For severity of fatty liver, there was no statistically significant association between vitamin D deficiency and incidence or severity of non alcoholic fatty liver in type 2 diabetes patients (P=0.06). Moreover, there was no significant difference in biochemical indices between type 2 diabetes patients with vitamin D deficiency and normal vitamin D level (P>0.05).

Treatment with vitamin D had no significant effect on AST, ALT, triglyceride, and FBS (P>0.05). HDL, ALP, and hemoglobin A1c decreased after treatment but the decrease was not statistically significant (P>0.05). Only serum levels of cholesterol and LDL decreased significantly in the patients undergoing treatment compared to the control group (P<0.001).

In the present study to investigate the association between vitamin D deficiency and incidence of non alcoholic fatty liver in the patients with type 2 diabetes and also to examine the efficacy of treatment with vitamin D in the type 2 diabetes patients with vitamin D deficiency and non alcoholic fatty liver referring a specialty clinic in Shahrekord, southwest Iran, the findings indicated that vitamin D deficiency was not associated with the incidence or severity of non alcoholic fatty liver. Also treatment with vitamin D had no significant effect on biochemical indices of liver function, FBS, and hemoglobin A1c and only serum levels of cholesterol and LDL decreased significantly in the patients undergoing treatment compared to the control group.

In the present study, vitamin D deficiency and duration of type 2 diabetes were not associated. In a study in the USA there was a significant difference in diabetes duration between the patients with and without vitamin D deficiency (26). Also another study indicated that the risk of diabetes was reported much higher in the patients with vitamin D deficiency than those with vitamin D normal levels (27). No association between vitamin D deficiency and duration of type 2 diabetes in the present study could be explained by including only the patients with definite diagnosis of diabetes (with at least six months of suffering diabetes) and no patients with recent diagnosis. If the study included the patients with a wider range of diabetes duration, then it was more likely to find an association between vitamin D deficiency and duration of type 2 diabetes.

No association of age and FBS with vitamin D deficiency was seen in type 2 diabetes patients, which is consistent with another study (27). However, inconsistent with the present study finding insignificantly higher hemoglobin A1c in the patients with vitamin D deficiency, Dalgard et al study of the patients with diabetes demonstrated this difference was significant (27). In addition the present study found no association between abdominal obesity and BMI in type 2 diabetes patients with vitamin D deficiency, which is consistent with Joergensen et al study but inconsistent with a meta analysis conducted to find an association between vitamin D deficiency and obesity. This meta analysis indicated that increase in BMI increased likelihood of vitamin D deficiency (28). Furthermore in a study, the association between vitamin D deficiency and abdominal obesity was confirmed (12). Since vitamin D is a fat-soluble vitamin and is reserved in adipose tissue, increased BMI in fatty individuals could decrease vitamin serum level by the vitamin D reserves in the body and cause the complications due to vitamin D deficiency (26). The association between metabolic syndrome and vitamin D deficiency was also investigated in the present study and no association was seen. Indeed, in the present study, metabolic syndrome-related parameters (waist circumference, triglyceride, HDL, and FBS) separately were not significantly associated with vitamin D deficiency, which is consistent with a meta analysis conducted in 2014. In this meta analysis of cross-sectional studies on the association between vitamin D level and metabolic syndrome, vitamin D level and metabolic syndrome were associated in short-term but longitudinal studies did not confirm such association (29).

Inconsistent findings on the association between vitamin D deficiency and incidence or severity of non alcoholic fatty liver was a motivation to conduct the present study. The findings indicated no significant association between vitamin D deficiency and incidence or severity of non alcoholic fatty liver in the patients with type 2 diabetes. This finding is consistent with a study of a Chinese population (13) and confirms lack of association between vitamin D deficiency and incidence or severity of non alcoholic fatty liver in some populations. Indeed a meta analysis of cross-sectional studies indicated the patients with non alcoholic fatty liver had lower serum vitamin D than normal individuals and the causal relationship between vitamin D deficiency and non alcoholic fatty liver has not been already explained adequately (13). In addition, the inconsistent findings of different studies could be due to differences in genetic and environmental factors.

In the present study, treatment with vitamin D in the patients with vitamin D deficiency and non alcoholic fatty liver indicated no effect on improvement of glycemia indices (FBS and hemoglobin A1c), which is consistent with other studies. For example, in a study of the effect of vitamin D on men using impaired glucose tolerance test, the findings indicated no significant change in FBS and hemoglobin A1c tests (30). Also a study on 10 women with type 2 diabetes of whom 70% had vitamin D deficiency, no significant improvement

of insulin resistance was reported in the patients receiving vitamin D despite decrease in insulin resistance (31).

In this study, treatment of type 2 diabetes patient with vitamin D efficiency and non alcoholic fatty liver with vitamin D supplementation caused a significant decrease in total cholesterol and LDL. In a meta analysis of vitamin D effect on lipid indices, consistent with the present study, a significant decrease in LDL level was reported but no significant change was reported for other lipid profile indices (32). The mechanism through which vitamin D causes improvement of lipid profile has not been yet known. Vitamin D exerts antioxidant effect which can lead to decreasing LDL and cholesterol (33-37). However, the antioxidant effect of vitamin D is unlikely to be the main cause of lipid profile improvement because antioxidants cause decrease in glucose, hemoglobin A1c, and diabetes complications, as well (38-41). But in the present study, sugar-related parameters did not charge.

The efficacy of vitamin D supplementation on improvement of fatty liver in type 2 diabetes patients with vitamin D deficiency and non alcoholic fatty liver indicated no treatment effect on AST, ALT, and ALP enzymes. Since these patients had vitamin D deficiency, vitamin D supplementation predictably caused decrease in ALP level and improvement of calcium hemostasis. Only one animal study has already demonstrated that increase in vitamin D causes decreased inflammation in hepatocytes, decreased fibrosis, and cell apoptosis (42).

A limitation of this study was the patients' unwillingness to participate in the study and follow up the treatment course. However, the significance of the study and its findings was explained to them to further their motivation to participate in the study and follow up the treatment course.

CONCLUSIONS AND RECOMMENDATIONS

The present study demonstrated no significant association between vitamin D deficiency and incidence or severity of non alcoholic fatty liver in the patients. However vitamin D supplementation to type 2 diabetes patients with non alcoholic fatty liver and vitamin D deficiency caused decrease in serum level of cholesterol and LDL. Therefore in light of vitamin D supplementation efficacy on cholesterol and LDL and since in studies with animals vitamin D has caused improvement of liver pathological indices except vitamin D serum level, study of non vitamin D-deficient individuals using other doses and/or active forms of vitamin D is recommended.

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