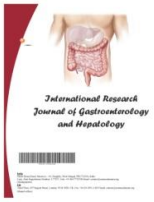

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Treatment Strategies for Nonalcoholic Fatty Liver Disease (NAFLD) Include Lifestyle Modifications and a Major Role of Vitamin D. A Randomized Controlled Trial

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Authors' contributions

This work was carried out in collaboration between both authors. Author MJK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author HG managed the analyses of the study. The two authors managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: hypovitaminosis D may be related to the pathogenesis of the nonalcoholic fatty liver disease (NAFLD) and may contribute to NAFLD's development and progression. Our study aimed to evaluate the therapeutic effects of vitamin D supplementation in patients with NAFLD.
Place and Duration of Study: Department of Gastroenterology, Affiliated Hospital of Inner Mongolia University for the Nationalities, China, between January 2020 and September 2020.
Methods: A total number of 166 patients were randomly divided into treatment group (n=86) and control group (n=80) with elevated levels of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) with hypovitaminosis D, with high or normal levels of T.G. (triglyceride), TCHO (total cholesterol), LDL-C (low-density lipoprotein C), HDL-C (high-density lipoprotein C). The treatment group received vitamin D 400 units twice a day along with lifestyle modifications as SMT

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(standard medical Treatment) (vitamin D+SMT), and the control group only received lifestyle modifications (SMT) for 6 months. The study's primary objective was to assess an improvement in elevated serum AST, ALT, T.G., TCHO, LDL-C, HDL-C, and the secondary purpose was to observe whether vitamin D can improve hypovitaminosis D in the patients with NAFLD.

Results: after 6 months of the treatment with vitamin D supplementation, a significant improvement in serum AST and ALT was observed in treatment group (vitamin D+SMT) when they were compared with control group (SMT) as, (ALT: vitamin D+SMT, 57.635±4.882 and 57.581±4.817(u/l) p value=0.033 vs SMT, 59.958±5.715 and 59.909±5.690(u/l) p value=0.07) and AST (AST: vitamin D+SMT, 46.920±4.162 and 46.864±4.145(u/l) p value=0.03 vs SMT, 50.270±4.060 and 50.256±4.053(u/l) p value=0.117). An improvement in vitamin D levels were observed only in treatment group (vitamin D+SMT) as, (VD: vitamin D+SMT, 20.985±3.732 and 21.049±3.684 (ng/ml) p value= 0.014 and SMT, 26.665±1.534 and 26.594±1.484 (ng/ml) p value=0.011).

Conclusion: In the patients with NAFLD, administration of vitamin D supplementation and lifestyle modifications can significantly improve serum ALT, AST, and vitamin D levels.

Keywords: NAFLD (nonalcoholic fatty liver disease); NASH (nonalcoholic steatohepatitis); SMT (standard medical Treatment); vitamin D; treatment.

1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is said to be the major cause of chronic liver disease. The disease encompasses a spectrum of clinical and histological patterns from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) in later stages [1]. NAFLD can be defined as the presence of 5% of the macrovascular steatosis in the absence of a secondary cause such as alcohol consumption and drugs [2]. The global burden of NAFLD is rising from simple steatosis to fibrosis and hepatocellular carcinoma [3]. The global prevalence of NAFLD was estimated as 25.24%, with the highest prevalence in the Middle East and South America and lowest in Africa [4]. NAFLD is said to be not only a disease among the obese population but also occurs in lean individuals and children [5-1]. Diagnosis of NAFLD can be made by an ultrasound or an elevated liver profile [6-7]. Recent studies have shown a very close relation between NAFLD and cardiovascular manifestations such as atherosclerotic CV (cardiovascular) disease, cardiac conduction system abnormalities, ischemic stroke and left ventricular hypertrophy [8]. Even though NAFLD is considered as a hepatic manifestation of metabolic syndrome (M.S.), the pathogenesis of NAFLD is not clearly understood yet, but some animal studies have shown an overload of primary metabolic substrate like (glucose, fructose and fatty acid) in the liver which leads to hepatocytes injury [1]. Recent evidence also points to the role of small intestine bacterial overgrowth, altered gut microbiota and endotoxemia [9-10]. Several treatment strategies were tried to treat NAFLD and NASH, such as vitamin E and C, hepatoprotective drugs such as ursodeoxycholic acid, pentoxifylline, orlistat, etc. [11]. And pioglitazone, rosiglitazone, pentoxifylline (PTX) methylxanthine derivatives, probiotics and silymarin which have shown a significant reduction in liver biochemistry such as AST, ALT [12]. Recent studies have shown a significant relation between serum vitamin D level and NAFLD, type 2 diabetes and metabolic syndrome [13]. Individuals with vitamin D deficiency are prone to have type 2 diabetes, M.S., and impaired glucose tolerance and insulin resistance (I.R.) [14]. Active vitamin D therapy could evaluate the development of NAFLD by inhibiting cell senescence, i.e., by inhibiting p53-p51 signaling pathway which shows a therapeutic potency for NAFLD in a rat model [15]. Vitamin D supplementation along with lifestyle modification could bring a very simple, cheap, and side effect free approach to the candidate and may reduce the burden of NAFLD and could prevent the progression of the disease to NASH, and hepatocellular carcinoma (HCC) which is said to be the end-stage disease. Till date there are very few randomized controlled trials of vitamin D supplementation in a patient with NAFLD. Therefore, we planned to study the therapeutic effects of vitamin D along with lifestyle modifications in a patient with nonalcoholic fatty liver disease.

2. METHODS

2.1 Participants

A total number of 200 patients were enrolled in this trial. Patients having elevated levels of ALT, AST, decrease levels of vitamin D (vitamin D level lower than <30 ng/ml) and normal or

elevated T.G., TCHO, HDL-C, LDL-C attending gastroenterology clinic at Inner Mongolia University for the Nationalities affiliated hospital department of internal medicine (gastroenterology) for a period of 1 year after obtaining an informed consent were enrolled in this study.

2.2 Criteria

2.2.1 Inclusion criteria

Patients age 18-70 years, Confirm diagnosis of NAFLD by an ultrasound, Individuals with hypovitaminosis D, Vitamin D levels <30 ng/ml , Elevated levels of ALT and AST, Elevated or normal levels of T.G., TCHO, LDL-C, and HDL-C, BMI either normal 18.5-24.9 kg/m^2 or above the normal levels.

2.2.2 Exclusion criteria

Patients with alcoholic liver disease, chronic hepatitis C, diabetes mellitus, chronic kidney disease, congestive cardiac failure, patients having any kind of malignancy, pregnant women, and patients who fail to follow the study protocols were excluded from our study.

BMI (body mass index) of the patients was calculated as kg/m^2 with weight in kilograms (kg) without any footwear and height in meters square (m^2) at erect position followed by the following formula, as weight in kilograms/height×height. (BMI was calculated According to Asian criteria-based body mass index) [16]. Fasting blood samples were taken from each patient and their vitamin D, T.G., TCHO, LDL-C, HDL-C, AST and ALT were measured. The diagnosis of NAFLD was made by ultrasonography by detecting hepatic steatosis.

2.3 Process

In the beginning of the trial, we had a total number of 200 Patients with NAFLD, during the trial 14 patients were excluded from the treatment group due to alcohol intake during trial and 20 patients were excluded from control group because of the lack of convenience to arrive in the hospital for follow up. Thus, we have a total number of 166 patients who were involved in this trial. The total number of patients in treatment group was (n=86) and total number of patients in control group was (n=80). The treatment group received vitamin D 400 units twice a day along with life style modification as SMT for the duration of 6 months and the control group only received SMT as lifestyle modifications, i.e., taking a low-calorie diet and carry out exercises on a daily basis for the duration of 6 months.

2.4 Statistical Analysis

Statistical analysis were performed using SPSS (version 17.0). Comparison between parameters pre- and post-vitamin D supplementation in patients with NAFLD was made by paired group t-test and P-value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Results

A total number of 166 patients were randomly divided into treatment group (n=86) and control group (n=80) as defined in methodology. The treatment group was treated with vitamin D+SMT and the control group was only treated with SMT. Both treatment and control groups were comparable at baseline regarding age, gender, BMI, vitamin D levels, T.G., TCHO, HDL-C, LDL-C, ALT, and AST. The detailed information about various parameter difference is shown in Table 1 and Table 2.

Table 3 represents changes in the various parameters after 6 months of the Treatment. Both of the groups were followed up after six months, and the changes in various parameters were evaluated after 6 months of the Treatment. A significant improvement were observed in BMI in both of the groups at six months (BMI: vitamin D+SMT, 25.595±1.941 and 25.539±1.939 (kg/m^2), p value=0.013 and SMT, as 26.665±1.534 and 26.594±1.484 (kg/m^2), p value=0.011). A significant improvement were observed in serum ALT and AST when compared with SMT group, (ALT: vitamin D+SMT, 57.635±4.882 and 57.581±4.817 (u/l), p value=0.033 and SMT, 59.958±5.715 And 59.909±5.690 (u/l), p value=0.070 and (AST: vitamin D+SMT, 46.920±4.162 and 46.864±4.145 (u/l), p value=0.030 and SMT, 50.270±4.060 and 50.256±4.053 (u/l), p value=0.117). Vitamin D levels were only improved in treatment group when compared with control group, vitamin D (VD: vitamin D+SMT, 20.985±3.732 and 21.049±3.684 (ng/ml) p value= 0.014 and SMT, 26.665±1.534 and 26.594±1.484 (ng/ml) p value= 0.086). Changes in metabolic parameters

Table 1. Description analysis of various parameters in treatment group (n=86)

	Min	Max	Mean	SD
Gender	**Female n (%)**		**Male n (%)**	
	40(46.5)		46(53.5)	
Age	21	61	42.78	10.99
BMI				
Baseline	19.40	28.90	25.60	1.94
At six months	19.40	28.90	25.54	1.93
VD				
Baseline	15.89	28.73	20.98	3.73
At six months	16.32	28.73	21.05	3.68
TG				
Baseline	.79	4.46	2.77	.93
At six months	.79	4.46	2.75	.93
TCHO				
Baseline	1.37	7.86	4.19	1.05
At six months	1.37	7.86	4.18	1.04
HDLC				
Baseline	1.09	2.79	1.48	.31
At six months	1.09	2.79	1.46	.31
LDLC				
Baseline	1.23	4.69	3.52	.75
At six months	1.23	4.67	3.52	.75
ALT				
Baseline	42.70	68.40	57.63	4.88
At six months	42.70	68.40	57.58	4.82
AST				
Baseline	20.70	56.60	46.92	4.16
At six months	20.70	55.30	46.86	4.14

Data are presented in this table as Mean ± S.D. and n (%). BMI (body mass index), V.D. (vitamin D), T.G. (triglyceride), TCHO (total cholesterol), HDL-C (high-density lipoprotein C), LDL-C (low-density lipoprotein C), ALT (alanine aminotransferase), AST (aspartate aminotransferase)

were observed in both groups as, (TG: vitamin D+SMT, 2.766±0.927 and 2.751±0.934 (mmol/l) p value=0.012 and SMT, 2.307±0.865 and 2.292±0.842 (mmol/l) p value=0.043). (TCHO: vitamin D+SMT, 4.194±1.046 and 4.189±1.040 (mmol/l) p value=0.019 and SMT, 5.027±0.808 and 5.021±0.804 (mmol/l) p value=0.021). (HDL-C: vitamin D+SMT, 1.476±0.305 and 1.464±0.308 (mmol/l) p value=0.019 and SMT, 1.608±0.195 and 1.595±0.178 (mmol/l) p value=0.023). (LDL-C: vitamin D+SMT, 3.516±0.754 and 3.512±0.752 (mmol/l) p value=0.022 and SMT, 3.550±0.408 and 3.534±0.402 (mmol/l) p value=0.026). Our results have demonstrated that vitamin D helps improve liver biochemistry and vitamin D levels itself in NAFLD subjects. Of the metabolic parameters like T.G., TCHO, HDL-C, LDL-C changes were observed in both of the groups, which suggests that lifestyle interventions like diet control and physical activity might be helpful to maintain metabolic parameters and BMI in the patients with NAFLD.

3.2 Discussion

This study is the first form of a randomized controlled trial in the department of internal medicine and gastroenterology in the affiliated hospital of Inner Mongolia University for the Nationalities. This study was designed to observe the therapeutic effects of vitamin D in NAFLD subjects. The results of our study suggest a very positive therapeutic effect of vitamin D on liver biochemistry and vitamin D levels were also improved in the subjects with NAFLD.

Vitamin D deficiency is a global health problem that affects more than 1 billion individuals worldwide [17]. Vitamin D deficiency is highly prevalent in china in older age adults when it was compared with the U.S. elderly population [18]. Vitamin D deficiency is common in all age groups including postmenopausal women around the world [19]. The prevalence of hypovitaminosis D in northeast central china was estimated as 69%

in men and 75% in women, and it's more common in winter [20]. There is a very significant relationship between low vitamin D levels, NAFLD, and NASH due to its "pleiotropic" functions and a role in cell differentiation and proliferation, regulation of inflammation, and immune modulation [21]. The primary role of vitamin D in the regulation of bone metabolism and calcium hemostasis and it plays a very significant role against liver fibrogenesis. The exact mechanism of vitamin D action in improving liver fibrosis still remains unknown, but it has been hypothesized that vitamin D possesses an anti-fibrotic activity on hepatic stellate cells through vitamin D receptor-mediated specific signal transduction pathways, which leads to inhibit the expression of pro-fibro genic genes [22]. A recent study has evaluated a relationship between low serum vitamin D levels and liver fibrosis in biopsy-proven NAFLD where serum vitamin D levels were ≤20 ng/mL among all NAFLD subjects and was independently associated with biopsy-proven NAFLD [23]. A clinical study shows a very significant relationship between low vitamin D levels and NAFLD in children age between 2-18 years in a biopsy-proven NAFLD where vitamin D levels were categorized as, deficient (≤ 20 ng/mL), insufficient (21-29 ng/mL), and sufficient (≥ 30 ng/mL) [24]. A cohort of biopsy-proven NAFLD subjects shows a high prevalence of hypovitaminosis D in 193 out of 234 subjects [25].

The role of bile acids in the disease progression of NAFLD cannot be avoided, as bile acids regulate metabolism and inflammation through nuclear farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5), where these receptors are the activators of transcriptional networks and signaling cascades which controls the expression of the genes which are involved in lipid, bile acid, carbohydrate metabolism and inflammation regulation [26]. The animal model study suggests that vitamin D treatment in rates increases the hepatic portal bile acid concentration, which elevates the

Table 2. Description analysis of various parameter in control group(n=80)

	Min	Max	Mean	SD
	Female n (%)		Male n (%)	
Gender	38(47.5)		42(52.5)	
Age	21	58	43.53	10.25
BMI				
Baseline	22.40	29.60	26.67	1.53
At six months	22.40	28.80	26.59	1.48
VD				
Baseline	16.34	28.92	21.84	3.52
At six months	16.34	28.92	21.86	3.52
TG				
Baseline	1.22	4.46	2.31	.86
At six months	1.22	4.44	2.29	.84
TCHO				
Baseline	1.44	6.22	5.03	.81
At six months	1.44	6.22	5.02	.80
HDLC				
Baseline	1.22	2.29	1.61	.19
At six months	1.22	2.29	1.59	.18
LDLC				
Baseline	2.26	4.48	3.55	.41
At six months	2.26	4.48	3.53	.40
ALT				
Baseline	51.4	68.9	59.96	5.72
At six months	51.4	68.9	59.91	5.69
AST				
Baseline	42.4	57.4	50.27	4.06
At six months	42.4	57.4	50.26	4.05

Data are presented in this table as Mean ± S.D. and n (%). BMI (body mass index), V.D. (vitamin D), T.G. (triglyceride), TCHO (total cholesterol), HDL-C (high-density lipoprotein C), LDL-C (low-density lipoprotein C), ALT (alanine aminotransferase), AST (aspartate aminotransferase)

Table 3. Changes in various parameter after 6 months of Treatment in SMT + Vitamin D (n=86) and SMT (n=80) groups

			Paired difference		
Characteristic	**Baseline (mean±SD)**	**At six months (mean±SD)**	**Mean±SD**	**t- value**	**p- value**
BMI(kg/m2)					
SMT+Vitamin D	25.595±1.941	25.539±1.939	0.056±.205	2.525	.013
SMT	26.665±1.534	26.594±1.484	0.071±.243	2.617	.011
VD(ng/ml)					
SMT+Vitamin D	20.985±3.732	21.049±3.684	.637±.235	2.515	.014
SMT(n=80)	21.845±3.521	21.870±3.517	.025±.130	1.737	.086
TG(mmol/l)					
SMT+Vitamin D	2.766±.927	2.751±.934	.014±.052	2.554	.012
SMT	2.307±.865	2.292±.842	.015±.063	2.061	.043
TCHO(mmol/l)					
SMT+Vitamin D	4.194+-1.046	4.189±1.040	.012±.045	2.490	.019
SMT	5.027±.808	5.021±.804	.009±.036	2.388	.021
HDL-C(mmol/l)					
SMT+Vitamin D	1.476±.305	1.464±.308	.012±.046	2.391	.019
SMT	1.608±.195	1.595±.178	.013±.049	2.320	.023
LDL-C(mmol/l)					
SMT+Vitamin D	3.516±.754	3.512±.752	.013±.046	2.342	.022
SMT	3.550±.408	3.534±.402	.016±.064	2.265	.026
ALT(u/l)					
SMT+Vitamin D	57.635±4.882	57.581±4.817	.535±.228	2.172	.033
SMT	59.958±5.715	59.909±5.690	.049±.237	1.839	.070
AST(u/l)					
SMT+Vitamin D	46.920±4.162	46.864±4.145	.056±.234	2.208	.030
SMT	50.270±4.060	50.256±4.053	.014±.078	1.586	.117

*BMI (body mass index), V.D. (vitamin D), T.G. (triglyceride), TCHO (total cholesterol), HDL-C (high-density lipoprotein C), LDL-C (low density lipoprotein C), ALT (alanine aminotransferase), AST (aspartate aminotransferase). * P-value <0.05 was considered as statistically significant*

expression of farnesoid X receptors thus leads to decrease lipogenesis and prevent the development of NAFLD [27].

A clinical trial with vitamin D supplementation in patients with NAFLD demonstrated a significant reduction in serum alkaline phosphatase ($P < 0.05$) and gamma-glutamyl transferase [28]. While another pilot study also has demonstrated the effect of vitamin D on liver biochemistry over the Treatment of 48 weeks, there was a significant improvement in serum ALT in the patients with histologically proven NASH [29]. As there are limited data available regarding the therapeutic effects of vitamin D in the subjects with NAFLD and NASH, most of the data comes from animal model studies [30].

Results of our trial suggested that vitamin D supplementation has a major role in NAFLD subjects. Vitamin D supplementation along with lifestyle modifications has a significant effect on liver biochemistry. A significant improvement was observed in serum ALT and AST and vitamin D levels were also improved in the treatment group when they were compared with the control group. As aminotransferases are the key indicators of hepatic inflammation and hepatocytes injury, both acute and chronic liver injury can lead to an elevated level of AST and ALT [31]. Recent studies have revealed a relation between vitamin D, serum ALT, and AST. A large number of 988 individuals with elevated levels of serum AST and ALT were treated with a high dose of vitamin D (50,000IU) and a very significant reduction was observed in serum AST and ALT [32]. Thus, vitamin D supplementation improves liver biochemistry and improves oxidative stress, and prevents hepatocytes injury. Apart from liver biochemistry, our study has demonstrated a significant improvement in the BMI of the patients in both groups. Other metabolic parameters like, T.G., TCHO, HDL-C, and LDL-C have shown an improvement in both groups, which suggests that the treatment group was not superior to the control group in terms of BMI, T.G., TCHO, HDL-

C, and LDL-C. Improvement in T.G., TCHO, HDL-C, and LDL-C might be due to diet control and physical activity.

The limitations of our study were that the diagnosis of NAFLD was made by ultrasound with the presence of significant liver fat, elevated AST, ALT, and elevated or normal levels of blood T.G., TCHO, HDL-C, and LDL-C which suggests hyperlipidemia in patients with NAFLD. There was no biopsy and histological evaluation of the disease. The dose of vitamin D (400IU) twice a day was not standardized, so the adequacy of vitamin D cannot be assessed in the patients.

4. CONCLUSION

Our study demonstrated that hypovitaminosis D is very common in patients with NAFLD, and it is also common in children, adults, and older ages. Vitamin D supplementation is safe in patients with NAFLD and it leads to a decrease in an elevated level of AST, ALT, and improve vitamin D levels in patients with NAFLD. Hypovitaminosis D is very common in the patients with NAFLD, and it is also common in children, adults and older ages. Vitamin D supplementation is safe in the patients with NAFLD and it leads to decrease an elevated level of AST, ALT, and improves vitamin D levels in patients with NAFLD.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this article. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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