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Vitamin D Effect on Ultrasonography and Laboratory Indices and Biochemical Indicators in the Blood: an Interventional Study on 12 to 18-Year-Old Children with Fatty Liver

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ABSTRACT

Purpose: The rising prevalence of childhood obesity in the past decades has caused non-alcoholic fatty liver disease (NAFLD) to become the most common cause of pediatric chronic liver disease worldwide. This study was aimed at determining the effect of vitamin D (Vit D) on ultrasonography and laboratory indices of NAFLD and some blood biochemical indicators in children.
Methods: In this interventional study liver ultrasonography was performed in 200 children with overweight and obesity. A 108 had fatty liver among which 101 were randomly divided into two groups of study (n=51) and control (n=50). The study group was treated with Vit D, 50000 U once a week whereas the control group received placebo with the same dose and package, both for 12 weeks. At the end of the intervention lab tests and ultrasound study was performed once again to evaluate the response to treatment.
Results: It was found out that Vit D supplementation improved the fatty liver grade in the study group. The mean changes in hemoglobin (Hb), uric acid, highdensity lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin, albumin and alanine aminotransferase (ALT) was significantly higher in the study group compared to controls (p<0.05). After the intervention and means adjustment, a significant difference was obtained in HDL-C, insulin, LDL-C and homeostasis model assessment of insulin resistance (HOMA-IR) between the two groups.
Conclusion: Vit D supplementation in addition to improving the fatty liver grade in ultrasonography and increasing the blood Vit D level, increases the HDL and Hb level besides decreasing uric acid, LDL, HOMA-IR, insulin and ALT levels.

Keywords: Child; Liver; Enzymes; Non-alcoholic fatty liver disease; Overweight; Obesity; Vitamin D

Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Given the changes in the living conditions, the incidence of obesity has been increasing at an alarming rate in most societies; children and adolescents are not an exception in this respect [1]. Obesity has even been declared an epidemic by the World Health Organization [2]. Based on numerous studies, it is estimated that over 155 million people suffer from overweight and obesity worldwide; 30 to 45% of these cases account for obese children [3]. The complications related to childhood obesity occur during childhood and adolescence and remain until adulthood.

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in the United States and probably the world. The number of affected cases are on a rapid rise and the disease can be considered as an epidemic disorder. Currently, NAFLD is regarded as the hepatic manifestation of the Metabolic Syndrome (MetS) [4], which in turn has been well recognized as a highly atherogenic condition [5,6]. It is one of the most common etiologies for a rise in liver enzymes in patients with no clinical manifestations [7]. In Western countries, the prevalence of NAFLD is 20 to 30% in the pediatric population and 70 to 80% in obese children [8].

NAFLD is a relatively progressive and chronic liver disease. Its advanced form is regarded as non-alcoholic steatohepatitis which is considered as one of the main causes of cryptogenic cirrhosis (up to 20%) [6]. Its prevalence in children ranges from 42.6 to 77.1% in different studies; it is expected that fatty liver will be the most common chronic liver disease in children in the near future [9,10]. This issue is of greater importance knowing that these children can turn into adults with cirrhosis, chronic hepatic failure and hepatocellular carcinoma in the next 10–30 years [11].

Treatment of fatty liver is based on the correction of risk factors such as obesity, diabetes and hyperlipidemia besides improving insulin resistance. The treatment is often selected based on its efficacy, safety and costs [11]. At present the standard treatment includes gradual weight loss (at least 10%) specially focused on losing lumbar obesity by improving the life style, more physical activity and changes in the daily diet [12].

It has been suggested that vitamin D (Vit D) deficiency may predispose an individual to glucose intolerance, altered insulin secretion and type 2 diabetes mellitus [13]. In recent years several studies have reported that Vit D deficiency is common in patients with NAFLD and importantly, it is associated with increased risk of steatosis, necroinflammation and fibrosis in both adults and children with biopsy-proven NAFLD [8,10,11]. Vit D receptors also act as a regulator of inflammation and oxidative stress in different body tissues [13-15]. Accordingly, ultrasound can provide useful information not only for the diagnosis but also for the grading of NAFLD. Therefore in this study we aimed to investigate the role of Vit D supplementation on changes in ultrasonography indices and blood biochemical markers in children with NAFLD.

MATERIALS AND METHODS

In this double-blind randomized-controlled clinical trial, the study population consisted of 12–18 year-old children with fatty liver. They all underwent ultrasonography by a single radiologist for confirming the diagnosis.

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In total 107 out of the 200 studied obese children had fatty liver. The children with overweight and obesity were classified based on the Centers for Disease Control and Prevention criteria; those with a body mass index (BMI) between 85–94th percentile were considered as overweight and a BMI ≥95th percentile as obese. Children with the mentioned criteria along with fatty liver and a Vit D level <30 ng/mL were enrolled in the study.

All cases with other causes of obesity such as Cushing's disease, hyperthyroidism, pseudo hypoparathyroidism and the chronic use of any drug or hepatitis due to any other etiology (hereditary disease or viruses) were excluded from the study.

Based on the study by Foroughi et al. [16] and the mean aspartate aminotransferase (AST) level in the Vit D group before and after the intervention and considering a study power of 80%, 50 cases were selected for each group. Among the students with confirmed fatty liver disease, 101 cases who fulfilled the inclusion criteria were selected and randomly divided into two groups: study (n=51) and control (n=50).

The children in the study group received Vit D capsules, a 50000 U Perl once a week for 12 weeks. The placebo group received placebo with the same dosage, color and package and for the same duration.

In the next step the effect of Vit D on lab indices of fatty liver and some of the blood biochemical indicators in such children was studied. A 5 mm blood sample was taken at fasting from all patients before and after the intervention and the provided serum was used for the tests analyses. Liver enzymes tests (AST, alanine aminotransferase [ALT], and alkaline phosphatase [ALP]), blood fat profile (low-density lipoprotein [LDL], highdensity lipoprotein [HDL], triglycerides [TG], and cholesterol [C]), Uric acid, albumin and fast blood sugar (FBS) were measured by the enzymatic method with the Roche kit (Cobas-Integra; Roche Diagnostics, Mannheim, Germany).

Serum Vit D and insulin were measured by the enzyme colorimetric assay and with the Roche kit (Cobas E.411, Roche Diagnostics); CBC was measured by the cell counter with the Sysmex solution and the Sysmex KX-2, whereas C-reactive protein (CRP) was measured quantitatively.

In the final stage, ultrasound study was done by the same radiologist who was blind to the patients' group allocation.

In this study all cases showing an improvement of at least one grade in the fatty liver grading in comparison to that before the study were regarded as improvement.

The study protocol was approved by the Ethics Committee of Birjand University of Medical Sciences (ir.bums.REC.1396) and was registered by the following code: IRCT2017082017756N23. An informed consent was obtained from each participant prior to study entrance.

Statistical analyses

SPSS Statistics for Windows, Version 15.0. (SPSS Inc., Chicago, IL, USA) was used for data analyses. The normality of data distribution was studied with the Kolmogorov-Smirnov test. In order to eliminate the effect of confounding factors the analyses of covariance was used. In case of normal data distribution parametric tests and for non-normally distributed data non-

parametric tests such as the Spearman's correlation coefficient were applied. To compare the frequency distribution of the fatty liver grade in the two groups before and after the study Fisher's exact test was used. The significance level was set at $p<0.05$.

RESULTS

In total 101 cases were studied. The two groups were similar in terms of age and sex ($p>0.05$, **Table 1**). Following the intervention, the fatty liver grade in 42 (82.4%) and 20 (40%) children in the study and control group improved respectively, indicating a significant difference ($p<0.001$). The results showed no significant difference in the mean level of blood biochemical indicators (white blood cell, platelet, hemoglobin [Hb], FBS, uric acid, Cholesterol [C], TG) before and after the intervention ($p>0.05$).

However, the mean level of HDL-C, LDL-C, insulin and albumin was significantly different between the two groups before the intervention. The mean changes in serum Hb, uric acid, HDL-C, LDL-C, insulin and albumin level after the intervention was higher in the study group compared to the controls. No such difference was observed for other biochemical indicators (**Table 2**).

Based on the obtained results, the mean level of liver enzymes (AST, ALT, and ALP) and CRP was not significantly different between the two groups before and after the intervention. However, the mean Vit D level after the intervention was significantly higher in the study group compared to controls ($p<0.001$). Accordingly, the mean changes in the hepatic level of ALT and Vit D was significantly higher in the study group compared to controls ($p=0.03$, $p<0.001$). However, the mean changes in AST, ALP, and CRP did not significantly differ between the two groups after the intervention (**Table 3**).

Given that the mean level of HDL-C, LDL-C, insulin, albumin, homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β was significantly different between the two groups before the intervention, in order to eliminate the confounding effect of the preintervention score, the analyses of covariance was used; it showed a significant increase in the mean HDL-C and decrease in the LDL-C, insulin and HOMA-IR level after the intervention and after adjustment in both groups, yet no such difference was observed for albumin and HOMA-β.

Table 1. Comparison of the study and control groups in terms of age and sex

Variable	Study	Control	*p*-value
Sex			0.09
Male	23 (45.1)	31 (62.0)	
Female	28 (54.9)	19 (38.0)	
Age (yr)			0.07
12–13	33 (64.7)	22 (44.0)	
14–15	11 (21.6)	13 (26.0)	
16–18	7 (13.7)	15 (30.0)	

Values are presented as number (%).

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Table 2. Comparison of blood biochemical markers before and after the intervention inside each group and between the two groups

Variable	Group	Before	After	*p*-value	Difference (after-before)
WBC	Study	8.18±1.78	7.85±1.48	0.09***	−0.33±1.49
	Control	8.30±2.34	7.87±1.91	0.19***	−0.44±1.94
p-value		0.83*	0.77*	-	0.90*
Hb	Study	14.40±1.25	14.95±1.10	<0.001***	0.55±0.65
	Control	14.87±1.56	14.74±1.30	0.08***	−0.13±0.68
p-value		0.10*	0.38*	-	0.001*
PLT	Study	295.14±55.90	307.37±59.48	0.004***	12.23±27.11
	Control	309.06±84.38	319.66±70.77	0.05***	10.60±38.26
p-value		0.62*	0.43*	-	0.88*
FBS	Study	93.80±7.39	93.84±6.39	0.97****	0.04±8.36
	Control	91.66±6.55	94.46±6.02	0.003****	2.80±6.34
p-value		0.13**	0.62**	-	0.07**
Uric acid	Study	5.63±1.31	5.35±1.15	0.003***	−0.28±0.67
	Control	5.67±1.50	5.74±1.41	0.40***	0.07±0.70
p-value		0.98*	0.12*	-	0.007*
Cholesterol	Study	160.41±31.28	163.18±31.54	0.31****	2.76±19.35
	Control	164.56±29.25	172.74±35.27	0.005****	8.18±19.54
p-value		0.49**	0.15**	-	0.17**
TG	Study	138.73±61.99	121.88±42.72	0.02***	−16.84±48.78
	Control	148.16±65.46	134.04±57.91	0.08***	−14.12±46.42
p-value		0.49*	0.39*	-	0.72*
HDL-C	Study	37.08±10.31	43.12±10.54	<0.001***	6.04±7.02
	Control	39.50±7.07	41.50±6.64	0.005***	2.0±4.62
p-value		0.03*	0.92*	-	<0.001*
LDL-C	Study	105.14±28.16	92.86±25.29	<0.001***	−12.27±16.31
	Control	93.96±23.75	96.80±27.45	0.31***	2.84±17.66
p-value		0.04*	0.47*	-	<0.001*
Insulin	Study	27.19±11.35	22.94±8.86	0.007***	−4.25±9.59
	Control	22.20±9.46	23.61±9.06	0.12***	1.41±7.97
p-value		0.02*	0.77*	-	0.002*
Albumin	Study	4.46±0.30	4.64±0.23	<0.001***	0.18±0.32
	Control	4.61±0.32	4.62±0.34	0.36***	0.01±0.34
p-value		0.002*	0.71*	-	0.001*

Values are presented as mean±standard deviation.
WBC: white blood cell, Hb: hemoglobin, PLT: platelet, FBS: free blood sugar, TG: triglycerides, HDL-C: highdensity lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, -: not available.
*Mann-Whitney U-test, **Independent *t*-test, ***Wilcoxon test, ****Paired *t*-test.

Table 3. Comparison of Vit D, CRP and liver enzymes before and after the intervention in the two groups

Variable	Group	Before	After	*p*-value	Difference (after-before)
AST	Study	24.65±7.36	23.20±10.67	0.001***	−1.45±9.10
	Control	24.06±7.15	22.92±8.29	0.14***	−1.14±4.65
p-value		0.62*	0.89*	-	0.09*
ALT	Study	29.66±15.26	27.55±17.41	0.01***	−2.10±10.48
	Control	27.15±12.81	27.15±15.28	0.94***	−0.002±8.92
p-value		0.54*	0.92*	-	0.03*
ALK	Study	219.63±99.68	211.25±103.79	0.10****	−8.37±35.70
	Control	221.68±96.02	219.78±108.96	0.71****	−1.90±35.53
p-value		0.92**	0.69**	-	0.36**
CRP	Study	2.40±2.60	2.26±2.12	0.74***	−0.14±2.42
	Control	2.11±2.13	3.55±6.21	0.05***	1.44±5.30
p-value		0.95*	0.93*	-	0.35*
Vit D	Study	9.78±6.31	29.94±6.34	<0.001***	17.17±6.22
	Control	11.29±5.49	13.13±4.80	<0.001***	1.84±3.91
p-value		0.08*	<0.001*	-	<0.001*

Values are presented as mean±standard deviation.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALK: alkaline, CRP: C-reactive protein, Vit D: vitamin D, -: not available.
*Mann-Whitney U-test, **Independent *t*-test, ***Wilcoxon test, ****Paired *t*-test.

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DISCUSSION

The increasing incidence of obesity in children is a significant risk factor for nonalcoholic fatty liver disease and obesity-associated morbidity. NAFLD in childhood is an evolving condition, potentially affecting many extra-hepatic organs; it requires a multidisciplinary approach to its treatment. NAFLD could be considered as a marker of subclinical atherosclerosis as well as a strong cardiovascular risk factor even at a very early age [6]. Besides obesity, it is primarily associated with metabolic diseases such as insulin resistance or diabetes mellitus, dyslipidemia and hypertension. The prevalence of MetS has been reported as 31.9 to 34.2% among obese Iranian children [17]. Accordingly, the prevalence of fatty liver in children ranges from 42.6 to 77.1% in different studies [9,10]. On the other hand, Vit D has a major role in bone mineral metabolism along with antimicrobial and antioxidant properties [2].

In this study we aimed to investigate the effect of Vit D supplementation on ultrasonography indices and blood biochemical indicators in children with fatty liver. Based on the postinterventional ultrasound results, the severity of fatty liver showed 1–2 grades of improvement after the intervention in 82.4% and 40% of the cases and controls, respectively, indicating a therapeutic effect for Vit D (p<0.001). In 4% of the controls it deteriorated by 1 grade indicating a statistically significant difference between the two groups (p<0.001). In Nobili et al. [18] study, on 73 overweight or obese children between the age of 8 to 18 years, it was concluded that the lower the Vit D level, the higher is the severity of liver fibrosis and that the serum level of Vit D has a direct relationship with nonalcoholic steatohepatitis and liver fibrosis in NAFLD children. Yildiz et al. [2], reported that the serum level of Vit D in obese children with hepatosteatosis is significantly lower than the Vit D level in obese children without hepatosteatosis. The results of the two latter mentioned studies are consistent with our findings.

The mean level of Vit D after the intervention was significantly higher in the study compared to the control group. In the studies by Maki et al. [19], Baziar et al. [20] and Foroughi et al. [16], the serum level of Vit D in the study group reached the normal range from the deficient level after the intervention as compared to the control group.

The findings of the current study showed that the mean change in the serum Hb level before and after the intervention is significantly higher in the study compared to the control group. In contrast to Han et al. [21] study, no direct relationship was found between Vit D effect and Hb level in women. However, in Sharma et al. [22] study iron deficiency anemia was more prevalent in the Vit D deficient group. This may be due to the fact that Vit D, by decreasing inflammatory cytokines, reduces the rate of inflammation-related anemia [22].

The mean changes in uric acid before and after the intervention was significantly higher in the study compared to the control group. This finding was consistent with that of Takır et al. [23], Peng et al. [24], Mohamed et al. [25] in which they all stated that low levels of Vit D are directly associated with high levels of uric acid, whereas in our study its level also decreased following the intervention.

The FBS level showed no meaningful difference between the two groups in post-intervention, similar to the study of Kelishadi et al. [26]. This finding may be due to the limited study population, and most cases having fatty liver of grade I or II. Such changes in FBS might

also occur in higher grades of fatty liver. In addition, the dosage and duration of Vit D consumption defines the difference observed in the results of our study with that of similar studies. In the study by Ashraf et al. [27], FBS had a direct correlation with Vit D level whereas after prescribing Vit D, a positive effect was achieved on the FBS. The same association was found in Gagnon et al. [28] and Foroughi et al. [16] studies. Vit D affects the FBS level by influencing the insulin secretion and its function, pituitary gland regulation and glucose hemostasis which can ultimately result in MetS development. It also adjusts the transcription of anti-inflammatory markers and insulin. In addition, Vit D regulates the level of calcium and phosphorus in the plasma and cytoplasm, therefore leading to increased intracellular glucose levels by increasing the intracellular calcium level [27].

Moreover, the mean change in the ALT level was significantly higher in the study compared to the control group; a finding similar to Rhee et al. [29] and Ashraf et al. [27] studies; but in contrast to Katz et al. [30] study. One of the hypotheses suggests that Vit D deficiency exacerbates NAFLD by activating the Toll-like receptors along with increasing inflammation and oxidative stress [29]. Reduced inflammation may result in reduced ALT levels.

The mean HDL-C level following intervention was also significantly higher in the study group, similar to Maki et al. [19] studies in which a direct association was found between HDL and serum Vit D level. Tavakoli et al. [31] also reported a rise in HDL-C by Vit D supplementation. However no such effect was achieved in Kelishadi et al. [26] Study.

Also significant negative association was obtained between Vit D supplementation and LDL-c changes in the present study. Also reported a significant inverse relationship between Vit D deficiency and BMI, serum cholesterol, TG and LDL-c. Nevertheless Kelishadi et al. [26] reported no effect in this respect. In general, MetS and obesity are associated with a decrease in HDL-c and an increase in TG and LDL-although the exact biological mechanism for linking Vit D deficiency to dyslipidemia risk is still weak, yet knowing that Vit D regulates the level of calcium and phosphorus in the plasma and cytoplasm, it is suggested that increased Vit D absorption decreases the absorption of fat in the intestines. In addition, the increased number of Vit D receptors increases the lipoproteins enzyme level which can decrease the TG level, highlighting the role of Vit D in reducing dyslipidemias [27].

A decrease in the insulin level was observed in our study, but HOMA-B was not influenced even after means adjustment. In the study by Foroughi et al. [16] Vit D supplementation resulted in HOMA-IR reduction in patients with fatty liver, similar to our study. However, insulin and HOMA-B was not affected remarkably. In Kelishadi et al. [26] study Vit D supplementation resulted in reduced insulin resistance and cardiac disease risk in obese children. Ock et al. [32] also reported that Vit D level has an inverse independent association with insulin resistance in the healthy non-obese women in Korea. However, Song et al. [33] concluded that Vit D has no independent effect on insulin resistance among Korean men and women.

Choi et al. [34] showed that the male sex is more susceptible to increased insulin resistance with Vit D deficiency in comparison to females. Although the two groups studied by Choi et al. [34] had equal sex ratios, the logistic regression results in their study well indicated the gender effects of increased insulin resistance in men. In our study, there was no significant difference in sex ratios between the two groups, either (p-value=0.09) and the post-intervention HOMA-IR level was significantly different. However, the insulin resistance levels in the two gender groups were not significantly different after the intervention.

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The evidence suggest that Vit D suppresses chronic inflammation which is associated with obesity and insulin resistance. NAFLD is associated with insulin resistance in both the liver and muscle tissues. Vit D can reduce the level of free fatty acids in insulin resistance in both the peripheral tissues and hepatocytes [35].

Mean changes in CRP showed no meaningful difference after the intervention between the two groups, similar to Foroughi et al. [16] study and in contrast to Amer and Qayyum [36] study.

The reason for the non-response in our study in comparison to other studies can be the small sample size and that most cases had a fatty liver of grade I and II. Therefore performing similar studies on a larger population, on higher grades of fatty liver and with a longer follow-up period is highly recommended.

Among the strong points of this study, the interventional setting can be mentioned. Interventional studies in this respect are rare and in most cases the correlation between Vit D and blood biochemical markers were studied in a case-control setting.

The main limitation of the present study was that the NAFLD diagnosis was based on observing steatotic fatty liver in ultrasonography and ruling out the other causes of hepatic steatosis along with ALT increase, but without a biopsy; whereas the standard diagnostic approach in such cases is liver biopsy. Moreover, the study was performed on a small population of children and the dose and duration of supplementation may have been insufficient, while no defined standard time course is mentioned for children in this respect. Furthermore, the difference in sex especially regarding the effect of sexual hormones in the mechanism of fatty liver disease, serum Vit D status, and gene polymorphism in relation to the disease could all play a role in this condition.

Vit D prescription, can increase the level of Hb and HDL besides decreasing uric acid, LDL, insulin, HOMA-IR and ALT levels. This shows that Vit D has a protective effect against NAFLD.

Taken together and given the many researches done and advances made in NAFLD, they are not yet applied in clinical practice. Early identification of NAFLD in childhood will allow for intervention with lifestyle modification and its early treatment will play a crucial role in avoiding end-stage liver disease.

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