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# Effects of vitamin D supplementation on the glycaemic indices, lipid profile and liver function tests in patients with cirrhosis: a double-blind randomised controlled trial

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## ABSTRACT

**Background** Liver cirrhosis is considered a progressive disease that can eventually result in death. Vitamin D deficiency is prevalent in patients with cirrhosis. Few studies have been conducted on the effect of vitamin D supplementation in patients with cirrhosis.

**Objectives** The aim of this study was to identify the effect of vitamin D supplementation on lipid profile, glycaemic indices and liver function tests in patients with cirrhosis.

**Methods** Sixty patients with cirrhosis were involved in this double-blind, randomised controlled clinical trial. During the intervention, patients received one 50 000 IU pearl of vitamin D supplement or placebo per week for 12 weeks. Before and after supplementation, we assessed serum 25-hydroxy-vitamin-D3 (25(OH) D3), glycaemic indices (insulin, haemoglobin A1c, fasting blood glucose (FBG) and homeostatic model assessment for insulin resistance (HOMA-IR)), lipid profile and liver function tests.

**Results** Baseline variables were not significantly different between groups. The present study indicated that over the 12 weeks, vitamin D supplementation significantly increased serum 25(OH) D3 ($p<0.001$), and also significantly decreased FBG ($p=0.006$), and HOMA-IR ($p=0.001$).

**Conclusions** Vitamin D supplementation significantly improves FBG and HOMA-IR as well as serum 25(OH) $D_3$ in patients with cirrhosis.

**Trial registration number** The protocol of the study was registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT20140502017522N2).

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To the best of our knowledge, there is no research on the impact of vitamin D supplementation on patients with cirrhosis in Iran, and this research is the first research in this context.

### WHAT THIS STUDY ADDS

⇒ The results of this study showed that vitamin D supplementation (50000 IU/week for 12 weeks) enhance serum 25(OH)D3 as well as reduce HOMA-IR, and FBG levels in patients with cirrhosis.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is recommended to evaluate serum 25(OH) D3 in patients with cirrhosis.
⇒ Vitamin D supplementation is proposed as a complementary therapy in patients with cirrhosis.

## INTRODUCTION

Liver cirrhosis is the last stage of chronic liver diseases (CLD) which progresses slowly over years. It can eventually lead to complete liver failure and death.[1] The prevalence of liver cirrhosis and its morbidity and mortality is increased, making it a main health concern globally.[1 2] Fatty liver disease (especially alcoholic fatty liver disease) and viral hepatitis (B or C) are the most common causes of cirrhosis.[1] Vitamin D, a fat-soluble vitamin, has a significant role in health maintenance.[3] It is necessary for calcium homeostasis[4] and also has a role to regulate the body's immune system.[5] Liver has an important role in vitamin D metabolism, and various research indicated that vitamin D deficiency (VDD) is related to an increased risk of some chronic diseases (such as type 2 diabetes and metabolic syndrome) and mortality.[6 7] Several studies showed that more than two-thirds of patients with CLD suffer from VDD.[8 9] A decreased number of hepatocytes and changes in the hydroxylation of vitamin D in the liver are some causes of VDD in patients with cirrhosis.[8] Kubesch *et al* reported an association between severe VDD and decompensated cirrhosis.[10] Few studies have been conducted on the effect of vitamin D supplementation in patients with cirrhosis. This study aimed to identify the effects of vitamin D supplementation on the serum

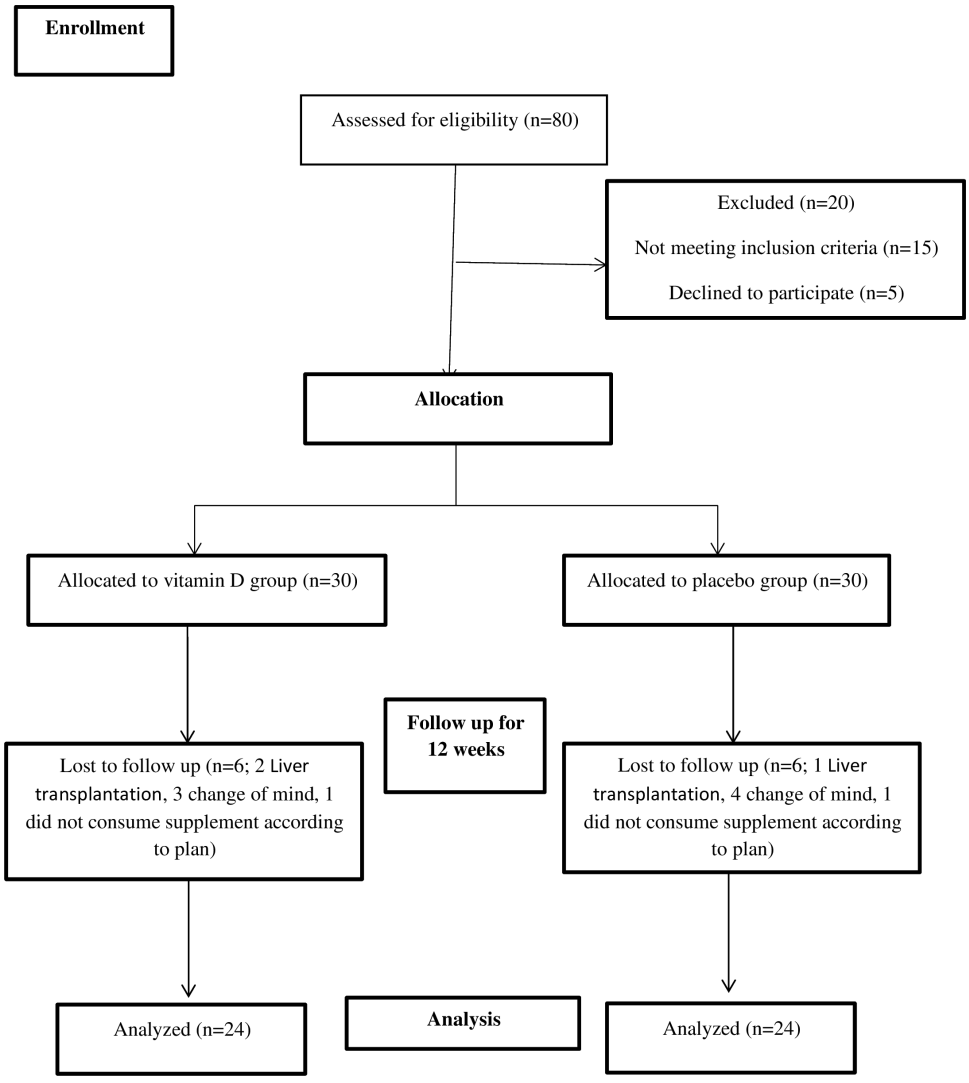


**Figure 1** Summary of subjects' flow.

25(OH) D3 as well as metabolic indices in patients with cirrhosis.

## MATERIALS AND METHODS

### Study design and participants

In order to compare vitamin D supplementation on serum 25-hydroxy-vitamin-D3 (25(OH) D3), glycaemic indices, lipid profile and liver function tests in patients with cirrhosis, a randomised double-blind placebo-controlled trial was done in Baqiyatallah Hospital, Tehran, Iran (from October 2019 to March 2020).

Participants who met the following inclusion criteria were included in the study: (1) diagnosis of cirrhosis (based on clinical characteristics, laboratory factors, medical imaging (abdominal ultrasonography and fibroScan) and endoscopic findings of varices); (2) age 18–70 years, (3) serum level of 25(OH)D3<50 ng/mL. The exclusion criteria included: (1) history of hepatocellular carcinoma or jejunostomy or gastroplasty bypass; (2) pregnancy or lactating; (3) serious injuries or chronic diseases such as type 2 diabetes, renal or heart failure, any type of malignancy, myocardial infarction and stroke; (4) multivitamin or vitamin D consumption for the past 3 months; (5) alcohol drinking; and (6) digestive disorders such as coeliac disease or steatorrhoea.

An informed consent form was signed by all of the participants. The protocol of the study was confirmed by the for Research at Baqiyatallah University of Medical Sciences (IR.Bmsu.REC.1397.039) and also registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT20140502017522N2).

Sixty patients were randomly assigned to either intervention (n=30) or placebo (n=30) group. The randomisation (15 blocks with sizes of 4) sequence was generated using a computer-generated list of random numbers. The concealment of the sequence ensured via the sealed and opaque envelopes. Patients were recommended to take either one oral pearl vitamin D supplement (50 000 IU) or placebo per week, for 12 weeks. For applying the blinding procedure in the study, the colour, packaging and shape of the placebo were analogous to the vitamin D supplements.

Table 1 Baseline characteristics of the study participants

| Variables | Vitamin D supplementation n=30 | Placebo n=30 | P value |
|---|---|---|---|
| Age (years) | 52.00±10.70 | 53.90±11.08 | 0.48 |
| Gender | | | 0.052 |
| Male N (%) | 17 (56.7) | 24 (80) | |
| Female N (%) | 13 (43.3) | 6 (20) | |
| BMI (kg/m$^2$) | 26.98±1.02 | 27.55±1.04 | 0.69 |
| HbA1C1 (%) | 5.55±0.24 | 5.92±0.24 | 0.33 |
| HOMA-IR (score) | 59.65±10.86 | 80.30±10.86 | 0.18 |
| Insulin (µIU/mL) | 13.06±2.07 | 17.08±2.07 | 0.17 |
| FBG (mg/dL) | 99.95±7.44 | 107.50±7.44 | 0.47 |
| Cholesterol (mg/dL) | 149.06±8.35 | 142.13±8.35 | 0.55 |
| Triglyceride (mg/dL) | 107.93±10.22 | 82.10±10.22 | 0.08 |
| HDL-C (mg/dL) | 41.08±2.45 | 42.05±2.45 | 0.78 |
| LDL-C (mg/dL) | 84.26±6.05 | 84.00±6.05 | 0.97 |
| AST (U/l) | 45.00±5.65 | 49.96±5.65 | 0.53 |
| ALT (U/l) | 36.63±5.14 | 41.10±5.14 | 0.54 |
| Serum 25(OH)$D_3$ (ng/mL) | 18.36±2.14 | 21.37±2.14 | 0.32 |

Data are shown as means±SE.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FBG, fasting blood glucose; HbA1C1, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; 25(OH) $D_3$, serum 25-hydroxy-vitamin-D3.

The participants were instructed not to change their level of physical activity as well as dietary intake during the study period. At the baseline as well as the end of the study, a 2-day (1 day off and 1 day on) 24-hour dietary recall questionnaire and a reliable and valid[11] scaled questionnaire, organised in nine multiple metabolic equivalent (MET) levels,[12] were completed by all participants. Moreover, a trained nutritionist contacted patients once a week for follow-up.

## Characteristics of the supplement

Vitamin D supplements (50 000 IU) and placebos used in this research were manufactured by Zahravi Pharmaceutical Company (Tabriz, Iran). The placebo (containing edible paraffin) was packaged in similar capsules.

## Anthropometric measurements

To measure the weight and height, a Seca digital scale (to the nearest 100 g, Seca, Germany) and a Seca stadiometer (the nearest 0.5 cm, Seca, Germany) were used, respectively. Body mass index (BMI) was computed by dividing the weight in kg by height in m$^2$.

## Laboratory tests

Blood samples were collected from the antecubital vein after 12 hours overnight fasting at the baseline and after 12 weeks of supplementation. Serum 25(OH)D3, glycaemic indices (insulin, fasting blood glucose (FBG), haemoglobin A1c (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR)), as primary outcome variables, and lipid profile (triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)) as well as liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), as secondary outcome variables, were measured in both groups.

Serum 25(OH)$D_3$ and insulin levels were determined via chemiluminescence immuneassay (DiaSorin, USA). FBG was measured by enzymatic glucose oxidase approach using a kit (Pars Azmoon Co., Tehran, Iran). HbA1c was measured by cation-exchange chromatography through a BioSystem kit (BioSystems SA, Barcelona, Spain). The levels of TG, TC and HDL-C were enzymatically measured by applying the same kit (Pars Azmoon Co.) by a Selectra ProM autoanalyzer (Netherlands). Serum ALT and AST enzymes were measured using the kit (Pars Azmoon Co.) by the photometric approach. All intra-assay and interassay coefficients of variation were <5%. LDL-C was computed applying the following formula LDL-C=TC – HDL-C – 0.16 (TG). HOMA-IR was determined by the formula [fasting insulin (mU/L) × fasting glucose (mg/dL)/405.[13]

## Statistical analysis

Considering a statistical power of 80% with a two-sided test with a type I error=0.05 and SD for the difference of serum 25(OH) $D_3$ concentration,[14] the sample size was determined as 22/group. Taking into account a 30% attrition rate, 60 patients were enrolled in the study.

Table 2 Nutritional intake and physical activity in two groups of vitamin D supplements and placebo

| | Intervention | Vitamin D supplements | Placebo | P value |
|---|---|---|---|---|
| Energy (kcal/day) | Pre | 1870.40±130.90 | 1852.36±127.55 | 0.92 |
| | Post | 1716.61±116.48 | 1664.43±90.23 | 0.72 |
| | P value | 0.19 | 0.19 | – |
| Fat (g/day) | Pre | 54.53±5.39 | 58.18±3.71 | 0.57 |
| | Post | 47.18±3.88 | 51.01±4.61 | 0.52 |
| | P value | 0.22 | 0.29 | – |
| Protein (g/day) | Pre | 91.4±10.10 | 94.64±12.71 | 0.84 |
| | Post | 75.34±7.94 | 76.88±10.09 | 0.90 |
| | P value | 0.27 | 0.12 | – |
| Carbohydrate (g/day) | Pre | 257.63±21.14 | 235.51±18.47 | 0.43 |
| | Post | 251.86±23.94 | 213.98±10.45 | 0.15 |
| | P value | 0.49 | 0.27 | – |
| Cholesterol (g/day) | Pre | 266.36±34.15 | 280.65±33.09 | 0.76 |
| | Post | 259.85±35.17 | 248.25±34.73 | 0.81 |
| | P value | 0.71 | 0.57 | – |
| Vitamin D (µg/day) | Pre | 1.44±0.23 | 1.47±0.21 | 0.92 |
| | Post | 1.02±0.20 | 1.42±0.17 | 0.14 |
| | P value | 0.14 | 0.59 | – |
| Physical activity (MET.h/day) | Pre | 38.46±1.22 | 37.87±0.69 | 0.68 |
| | Post | 39.33±1.46 | 36.23±0.63 | 0.06 |
| | P value | 0.86 | 0.11 | – |

Data are shown as means±SE.

Data were expressed as means±SE. The level of statistical significance level was set at 0.05. Statistical analyses were performed with STATA software V.13 (Stata Corp). Normality of the distribution of the variables was checked via Kolmogorov-Smirnov test. Baseline parameters were compared using $\chi^2$ test. Analysis of covariance was used to adjust the effects of confounding variables (baseline preintervention outcomes, sex and and preintervention serum 25(OH)$D_3$ level) on outcome measures. Independent Student's t-test was used to compare the differences between the mean values of the items studied in both groups. To compare the mean values of variables before and after the intervention in each group, a paired t-test was used.

## RESULTS

The current research was done on 60 patients with cirrhosis. No significant harm or side effect was identified during the study; hence, the research ended at the expected date. Cirrhosis was due to hepatitis B virus in 24 patients, hepatitis C virus in 15 patients, cryptogenic in 14 patients, autoimmune hepatitis in 5 patients and alcoholic and non-alcoholic steatohepatitis in 2 patients.

Twelve patients discontinued the intervention. Forty-eight patients (vitamin D group (n=24) and placebo group (n=24)) completed the research (figure 1). At the beginning and end of the study, infection, ascites, variceal bleeding and encephalopathy were not observed in any of the patients.

Regarding the baseline characteristics (demographic, biochemical and anthropometric data) and the dietary intake as well as physical activity, no significant difference was seen between the two study groups (tables 1 and 2).

Table 3 shows the effects of vitamin D supplementation on the outcome variables based on the crude and adjusted models. The vitamin D supplementation significantly increases the serum 25 (OH) $D_3$ before and after adjusting the covariates (p=0.0001). Moreover, the vitamin D supplementation significantly decreases FBG and HOMA-IR before (p=0.008 and p=0.0007, respectively) and after adjusting the covariates (p=0.006 and p=0.0017, respectively). Also, vitamin D supplementation decline insulin levels before and after adjusting the covariates (p=0.012 and p=0.085, respectively). The vitamin D supplementation did not change BMI, lipid profile and liver function tests before and after adjusting the covariates.

## DISCUSSION

According to our results, vitamin D supplementation led to a significant increase in serum 25(OH) D3 as well as a significant decrease in FBG and HOMA-IR in patients

**Table 3** Outcome distribution in Pre&Post intervention by study groups according to crude and adjusted models

| Variable | Model | Time | Vitamin D group | Placebo group | Mean difference (95% CI)* | P value† |
|---|---|---|---|---|---|---|
| Serum 25(OH)$D_3$ | Crude | Pre | 18.36±2. 14 | 21.37±2.14 | –3.00(–9.07 to 3.06) | **0.0001** |
| | | Post | 44.37±3.05 | 20.91±3.11 | 23.46 (14.69 to 32.23) | |
| | Adjusted | Post | 45.25±2.90 | 19.99±2.96 | 25.26 (16.71 to 33.80) | **0.0001** |
| FBG (mg/dL) | Crude | Pre | 99.95±7.44 | 107.50±7.44 | –7.54(– 28.62 to 13.53) | **0.008** |
| | | Post | 89.11±5.88 | 112.20±5.99 | –23.08 (–39.97 to –6.20) | |
| | Adjusted | Post | 90.62±4.73 | 110.62±4.83 | –19.99 (–33.94 to –6.03) | **0.006** |
| $HbA_1c$ (%) | Crude | Pre | 5.55±0.24 | 5.92±0.24 | –0.34 (–1.03 to 0.35) | 0.07 |
| | | Post | 5.41±0.22 | 5.99±0.22 | –0.58(– 1.21 to 0.05) | |
| | Adjusted | Post | 5.54±0.17 | 5.86±0.17 | –0.31(– 0.82 to 0.20) | 0.23 |
| Insulin (µIU/mL) | Crude | Pre | 13.06±2.07 | 17.08±2.07 | –4.00(– 9.88 to 1.85) | **0.012** |
| | | Post | 10.60±1.58 | 16.52±1.62 | –5.91 (–10.48 to –1.35) | |
| | Adjusted | Post | 12.03±1.15 | 15.04±1.17 | –3.00 (–6.43 to 0.43) | 0.085 |
| HOMA-IR (score) | Crude | Pre | 59.65±10.86 | 80.30±10.86 | –20.46(– 51.41 to 10.12) | **0.0007** |
| | | Post | 41.69±7.02 | 78.16±7.16 | –36.46 (–56.63 to –16.29) | |
| | Adjusted | Post | 47.07±5.20 | 72.57±5.31 | –25.49(–40.90 to –10.09) | **0.0017** |
| Cholesterol (mg/dL) | Crude | Pre | 149.06±8.35 | 142.13±8.35 | 6.93(– 16.70 to 30.57) | 0.24 |
| | | Post | 154.80±9.50 | 138.68±9.69 | 16.12(– 11.15 to 43.40) | |
| | Adjusted | Post | 150.42±6.40 | 143.23±6.53 | 7.18(– 11.81 to 26.17) | 0.45 |
| Triglyceride (mg/dL) | Crude | Pre | 107.93±10.22 | 82.10±10.22 | 25.83(– 3.10 to 54.76) | 0.26 |
| | | Post | 101.30±9.56 | 85.88±9.75 | 15.42(– 12.01 to 42.86) | |
| | Adjusted | Post | 90.42.±5.36 | 97.19±5.48 | –6.76 (–22.89 to 9.36) | 0.40 |
| HDL-C (mg/dL) | Crude | Pre | 41.08±2.45 | 42.05±2.45 | –0.96(– 7.90 to 5.98) | 0.74 |
| | | Post | 45.24±2.90 | 43.88±2.96 | 1.36(– 6.97 to 9.69) | |
| | Adjusted | Post | 46.50±2.30 | 42.57±2.35 | 3.93(– 2.85 to 10.72) | 0.24 |
| LDL-C (mg/dL) | Crude | Pre | 84.26±6.05 | 84.00±6.05 | 0.26(– 16.87 to 17.39) | 0.21 |
| | | Post | 83.23±5.81 | 72.85±5.92 | 10.37(– 6.30 to 27.05) | |
| | Adjusted | Post | 79.98±3.95 | 76.23±4.04 | 3.74(–8.00 to 15.49) | 0.52 |
| AST (U/l) | Crude | Pre | 45.00±5.65 | 49.96±5.65 | –4.96 (–20.98 to 11.05) | 0.27 |
| | | Post | 39.46±3.10 | 34.52±3.16 | 4.94(– 3.95 to 13.84) | |
| | Adjusted | Post | 39.79±2.73 | 34.16±2.79 | 5.62 (–2.43 to 13.69) | 0.16 |
| ALT (U/l) | Crude | Pre | 36.63±5.14 | 41.10±5.14 | –4.46 (–19.03 to 10.10) | 0.57 |
| | | Post | 33.69±2.76 | 31.44±2.81 | 2.25 (–5.67 to 10.17) | |
| | Adjusted | Post | 33.48±2.72 | 31.66±2.77 | 1.81 (–6.18 to 9.82) | 0.64 |
| BMI ($kg/m^2$) | Crude | Pre | 26.98±1.02 | 27.55±1.04 | –0.57 (–3.49 to 2.35) | |
| | | Post | 26.99±1.09 | 27.59±1.06 | –0.6 (–3.6 to 2.4) | 0.69 |
| | Adjusted | Post | 27.15±0.22 | 27.41±0.23 | –0.25 (–0.92 to 0.40) | 0.43 |

Data are shown as means±SE.
*Mean difference (95% CI) = vitamin D supplements - placebo. Adjusted for baseline preintervention outcome, sex and preintervention serum 25(OH)$D_3$ level (calculated based on one-way ANCOVA model).
†Calculated based on ANCOVA. Significant findings are in bold.
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; 25(OH) $D_3$, serum 25-hydroxy-vitamin-D3.

with cirrhosis. However, vitamin D supplementation did not show any significant effect on lipid profile and liver function tests in these patients.

Our results indicated that vitamin D supplementation significantly increase serum 25 (OH) $D_3$. These results are in line with the findings of other research.[15 16] The liver

has a major role in the synthesis of vitamin D. Not only the liver is the site of the first hydroxylation of vitamin D, but also vitamin D-binding protein is synthesised in the liver. The incidence of VDD increases with the progression of liver disease.[17] Arteh *et al* indicated that 29.5% of patients with cirrhosis suffer from severe VDD.[8] There is an inverse association between 25 (OH) $D_3$ levels and the stages of fibrosis.[18] Stokes *et al* reported that serum 25 (OH) $D_3 \leq 6$ ng/mL is an independent predictor of mortality among patients with cirrhosis.[19] Some studies reported that vitamin D may decrease liver damage due to its anti-inflammatory and antifibrotic properties.[5 19] On the other hand, due to the known role of vitamin D to maintain bone health and calcium metabolism, cirrhosis is associated with an increased risk of fractures.[20] Therefore, evaluation of serum 25(OH) $D_3$ among patients with cirrhosis is recommended.

Regarding the glycaemic indices, although vitamin D supplementation caused a significant decrease in FBG and HOMA-IR, a non-significant decrease in insulin and HbA1c was observed. These results are consistent with some previous researches.[21 22] Barchetta *et al* showed that vitamin D supplementation did not change FBG, insulin or HOMA-IR in patients with non-alcoholic fatty liver disease (NAFLD).[23] This inconsistency may be due to differences among the study population, kind of disease and duration of supplementation. Although there is not any agreement on the mechanism of the association between vitamin D and insulin resistance, some explanations exist: the presence of vitamin D receptors and 1-α hydroxylase in pancreatic β cells suggests a possible role of vitamin D in glucose homeostasis. So, VDD could lead to dysfunction of pancreatic β cells.[22] 1, 25$(OH)_2D_3$ elevates insulin production and secretion as well as expression of insulin receptors in pancreatic β cells and liver.[22 24] Moreover, vitamin D may increase insulin sensitivity by enhancing the calcium status. Calcium is needed for the release of insulin from pancreatic cells.[25] Also, elevated blood parathyroid hormone (PTH) is related to insulin resistance or glucose intolerance[25] and vitamin D may improve insulin function by lowering PTH levels.[26]

In line with other studies,[11 23 27] we found that the lipid profile did not change significantly after the vitamin D supplementation. The results of a meta-analysis showed that vitamin D supplementation had no significant effect on lipid profile in patients with NAFLD.[28]

According to the results of current research, although postintervention levels of both AST and ALT reduced, it was not significant; this finding is consistent with previous researches.[11 16 23 28 29] Furthermore, an epidemiological study indicated that the risk of elevated ALT, and AST is higher in patients with VDD.[30] Liver enzymes such as ALT and AST are common measurements for liver injury. Some studies indicated that VDD is associated with liver disease pathogenesis and severity.[9 17] VDD may lead to liver damage by increasing inflammation and fibrosis as well as decreasing the antiviral response.[18] As our searches shows, there is no clinical trial study that has investigated the effect of vitamin D supplementation on liver enzymes in patients with cirrhosis. The lack of significant effect in decreasing liver enzymes in our results could be due to low baseline values of ALT and AST. Vitamin D supplementation is more efficient on ALT and AST when their baseline levels are high.[29]

As far as our searches show, this is the first clinical trial aims to assess the effect of vitamin D supplementation on metabolic indices in patients with cirrhosis. Since Baqiyatallah Hospital is a reference hospital in Tehran metropolis, the finding of present study may be generalised to Iranian patients with cirrhosis. This study has two limitations. First, some variables including fibrosis and steatosis scores were not assessed due to budget constraints. Second, the sample size of the study was relatively small, so it is suggested to conduct studies with a larger sample size to investigate the side effects of supplementation of 50 000 IU vitamin $D_3$.

Our results indicated that the vitamin D supplementation (50 000 IU/week for 12 weeks) may enhance serum 25(OH)$D_3$ and reduce HOMA-IR, as well as FBG levels in patients with cirrhosis. Therefore, evaluation of serum 25(OH) $D_3$ and vitamin D supplementation (if needed) may recommend in patients with cirrhosis.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Ethics Committee for Research at Baqiyatallah University of Medical Sciences (IR.Bmsu.REC.1397.039). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request.

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## REFERENCES

1 Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: part 1 of a series on liver cirrhosis. *Dtsch Arztebl Int* 2013;110:85–91.
2 Bellentani S, Tiribelli C. The spectrum of liver disease in the general population: lesson from the Dionysos study. *J Hepatol* 2001;35:531–7.
3 Eliades M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease? *World J Gastroenterol* 2015;21:1718–27.
4 Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
5 Bikle DD. Vitamin D regulation of immune function. *Vitam Horm* 2011;86:1–21.
6 Pludowski P, Holick MF, Pilz S, *et al*. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* 2013;12:976–89.
7 Autier P, Boniol M, Pizot C, *et al*. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol* 2014;2:76–89.
8 Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010;55:2624–8.
9 Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol* 2007;5:513–20.
10 Kubesch A, Quenstedt L, Saleh M, *et al*. Vitamin D deficiency is associated with hepatic decompensation and inflammation in patients with liver cirrhosis: A prospective cohort study. *PLoS One* 2018;13:e0207162.
11 Kelishadi R, Rabiee K, Khosravi A, *et al*. Assessment of physical activity in adolescents of Isfahan. *Shahrekord Univ Of Med Sci J* 2004;3:55–66.
12 Aadahl M, Jørgensen T. Validation of a new self-report instrument for measuring physical activity. *Med Sci Sports Exerc* 2003;35:1196–202.
13 Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
14 Sharifi N, Amani R, Hajiani E, *et al*. Does vitamin D improve liver enzymes, oxidative stress, and inflammatory biomarkers in adults with non-alcoholic fatty liver disease? A randomized clinical trial. *Endocrine* 2014;47:70–80.
15 Fernández Fernández N, Linares Torres P, João Matias D, *et al*. Vitamin D deficiency in chronic liver disease, clinical-epidemiological analysis and report after vitamin d supplementation. *Gastroenterol Hepatol (Engl Ed)* 2016;39:305–10.
16 Pilz S, Putz-Bankuti C, Gaksch M, *et al*. Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations in Cirrhotic Patients: A Randomized Controlled Trial. *Nutrients* 2016;8:278.
17 Putz-Bankuti C, Pilz S, Stojakovic T, *et al*. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. *Liver Int* 2012;32:845–51.
18 Petta S, Cammà C, Scazzone C, *et al*. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010;51:1158–67.
19 Stokes CS, Volmer DA, Grünhage F, *et al*. Vitamin D in chronic liver disease. *Liver Int* 2013;33:338–52.
20 Bang UC, Benfield T, Bendtsen F, *et al*. The risk of fractures among patients with cirrhosis or chronic pancreatitis. *Clin Gastroenterol Hepatol* 2014;12:320–6.
21 Foroughi M, Maghsoudi Z, Askari G. The effect of vitamin D supplementation on blood sugar and different indices of insulin resistance in patients with non-alcoholic fatty liver disease (NAFLD). *Iran J Nurs Midwifery Res* 2016;21:100–4.
22 Pittas AG, Lau J, Hu FB, *et al*. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;92:2017–29.
23 Barchetta I, Del Ben M, Angelico F, *et al*. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *BMC Med* 2016;14:92.
24 Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. *Nutr Res Rev* 2009;22:82–92.
25 Malecki MT, Klupa T, Wanic K, *et al*. Vitamin D binding protein gene and genetic susceptibility to type 2 diabetes mellitus in a Polish population. *Diabetes Res Clin Pract* 2002;57:99–104.
26 Krall EA, Sahyoun N, Tannenbaum S, *et al*. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. *N Engl J Med* 1989;321:1777–83.
27 Dabbaghmanesh MH, Danafar F, Eshraghian A, *et al*. Vitamin D supplementation for the treatment of non-alcoholic fatty liver disease: A randomized double blind placebo controlled trial. *Diabetes Metab Syndr* 2018;12:513–7.
28 Tabrizi R, Moosazadeh M, Lankarani KB, *et al*. The effects of vitamin D supplementation on metabolic profiles and liver function in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndr* 2017;11 Suppl 2:S975–82.
29 Mansour-Ghanaei F, Pourmasoumi M, Hadi A, *et al*. The Efficacy of Vitamin D Supplementation against Nonalcoholic Fatty Liver Disease: A Meta-Analysis. *J Diet Suppl* 2020;17:467–85.
30 Skaaby T, Husemoen LLN, Borglykke A, *et al*. Vitamin D status, liver enzymes, and incident liver disease and mortality: a general population study. *Endocrine* 2014;47:213–20.