Review

Association of Vitamin D Status With Liver and Kidney Disease: A Systematic Review of Clinical Trials, and Cross-Sectional and Cohort Studies

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Abstract: *Background:* Vitamin D deficiency (VDD) is a major public health problem. There are few comprehensive systematic reviews about the relationship between Vitamin D status and liver and renal disease in Iran.
Methods: We systemically searched the following databases: Web of Science; PubMed; Cochrane Library; Scopus; Science Direct; Google Scholar and two Iranian databases (Scientific Information Database (SID) and IranMedex) up until November 2017 to identify all randomized control trials (RCTs), case control, cross-sectional and cohort studies investigating the association between vitamin D and any form of liver or kidney disease.
Results: Vitamin D insufficiency, or deficiency (VDD), is highly prevalent in Iran, reports varying between 44.4% in Isfahan to 98% in Gorgan. There is also a high prevalence of VDD among patients with liver or kidney disease, and the administration of vitamin D supplements may have beneficial effects on lipid profile, blood glucose, liver function and fatty liver disease, and bone health. Low serum vitamin D levels are related with abnormalities in these laboratory and clinical parameters.
Conclusion: VDD is prevalent in patients with chronic liver or renal disease in Iran. There appear to be several beneficial effects of vitamin D supplementation in vitamin D deficient patients with liver or kidney disease.

Keywords: Vitamin D deficiency, Liver disease, Kidney disease, Iran

Introduction

Vitamin D is an important micronutrient, that is essential in maintaining human health. It is a fat-soluble vitamin that plays important roles, acting via the vitamin D receptor [1]. Vitamin D has two principal forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_3 is produced by the action of ultraviolet irradiation on 7-dehydrocholesterol [2]. Although, humans can obtain vitamin D from dietary sources including dietary supplements, most vitamin D is derived from dermal synthesis [2]. It is metabolised to 25-hydroxyvitamin D (25-(OH) D) and subsequently to 1, 25 dihydroxyvitamin D (1, 25 $(OH)_2$ D), the active form of vitamin D, also known as calcitriol, by the action of liver and kidney enzymes [2].

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1, 25-$(OH)_2$ D regulates more than 200 genes via its nuclear receptors [3].

The cut-off values used to define vitamin D status are as follows: severely deficient a serum 25-(OH) D <30 nmol/L (12 ng/mL); moderately deficient 30–50 nmol/L (<20 ng/mL) and mildly deficient 50–75 nmol/L (30 ng/mL) [4]. These cut off value may differ geographically and this issue is addressed in the literature. The cut-off point has also been reported to be different based on gender [5]. Vitamin D deficiency (VDD) is an important public health problem. Based on epidemiologic studies, approximately one billion people globally suffer from VDD and its prevalence is increasing worldwide specially in Middle East region including Iran [6]. Traditionally, vitamin D is known as an important factor in metabolism of calcium and phosphorus but recent studies have demonstrated that low levels of vitamin D and VDD is associated with several diseases that include: hypertension and other cardiovascular disease, autoimmune disease, insulin resistance, diabetes, cancer, pulmonary disease, kidney and liver disease [4, 7].

There are several lines of evidence that indicate that vitamin D status is correlated with the incidence and progression of liver disease [8]. According to Martini et al., patients with non-alcoholic fatty liver disease (NAFLD), one of the most common chronic liver disease globally, have an association with vitamin D status and hepatic inflammation [9]. Inflammation is considered as an important feature of nonalcoholic fatty liver disease (NAFLD) and its progression. There is some evidence that vitamin D administration may control inflammation and preventing the progression of NAFLD to cirrhosis by [10].

Renal diseases are also related to vitamin D status. There are limited data on the incidence of chronic kidney disease (CKD) and micronutrient intake such as vitamin D [11, 12] but in a cohort study low vitamin D intake was correlated with CKD. On the other hand, low vitamin D in patients with CKD is related to disturbance of insulin secretion and also mineral homeostasis [13]. 1,25$(OH)_2$ D regulates the secretion of PTH [14]. The ability to produce 1,25$(OH)_2$ D is reduced in CKD. PTH rises and renal osteodystrophy may occur [3]. Impaired insulin secretion and glucose tolerance may also occur, which are risk factors for metabolic syndrome (MS), however vitamin D sufficiency is a protective factor against the development of MS [15].

We aimed to systematically review all available articles that have reported the associations between vitamin D and any type of liver or kidney disease studied in Iran up until November 2017. To our knowledge, this is the first systematic review evaluating clinical trials, observational and cohort studies conducted in the field of vitamin D status and supplementation in patients with any type of liver or renal disease in Iran.

Methods

Search strategy

We systemically searched the following databases: Web of Science; PubMed; Cochrane Library; Scopus; Science Direct; Google Scholar and two Iranian databases (Scientific Information Database (SID) and IranMedex), up until November 2017 (Figure 1). Our search was restricted to original papers in English and the Persian language. Since we wanted to find original articles conducted in Iran, we searched two Persian medical databases in Persian too: SID and IranMedex. In the search strategy for searching associated liver disease studies, we used the following words and medical subject headings (MeSH): "vitamin D" OR "vit D" OR "25(OH)D" AND liver OR "NAFLD" OR "non-alcoholic fatty liver disease" OR "fatty liver" OR "NASH" OR "non-alcoholic steatohepatitis" OR "hepatitis" AND "cirrhosis" AND Iran. To search for associated kidney disease studies, we used the following terms: "vitamin D" OR "vit D" OR "25(OH)D" AND "renal" OR "kidney" OR "renal transplant" OR "dialysis" OR "ESRD" AND Iran. It's noteworthy that we have concluded any acute or chronic liver and kidney disease in the literature. Also, the vitamin D status has been considered as if the authors has mentioned in their studies whether mild, moderate or severe deficiency of insufficiency. The search was performed by two independent researchers and the results were checked by a third researcher.

Data extraction

Data were extracted from selected articles, and included the last name of first author, publication year, city, study type, sample size including the population that withdrew, population characteristics, dose of administrated vitamin D, vitamin D concentration and its baseline level. Moreover, after intervention, technique of vitamin D measurement, study duration, and outcomes of the study were considered. Outcomes of interest were liver function tests (Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)) in the first search, which focused on the relationship between liver diseases and vitamin D; and PTH, calcium and phosphate, in the case of finding relation between kidney diseases and vitamin D. In order to obtain missing data that were not mentioned in the articles, we contacted the corresponding authors of the papers.

Quality assessment

In order to evaluate the quality of included studies, we used specific tools provided by the Joanna Briggs Institute for

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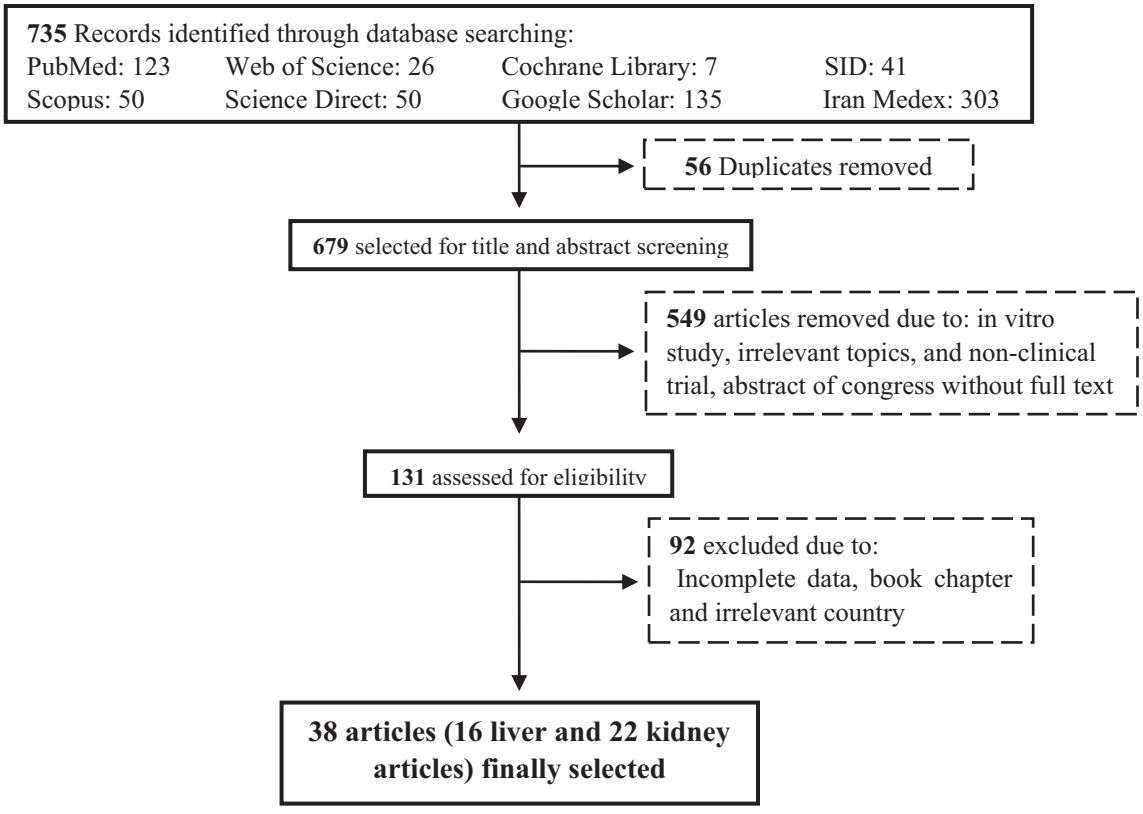

Figure 1. Flow chart of search strategy.

cross sectional and clinical trials [16, 17]. Data extraction and study quality assessment were performed independently by two reviewers. This assessment used a measuring scale, studies that scored 5 or more score are considered to be high quality.

Results

Characteristics of included studies in field of liver disease

Studies of patients with liver disease were evaluated with regard to vitamin D level in several studies in Iran. Studies based in the cities of Tehran and Isfahan were the most frequent in this field. Most of these studies were conducted on patients with NAFLD. Others included patients with cirrhosis, hepatitis, cholestasis and liver transplant. The mean age of adult patients evaluated in these studies was approximately 42 years. Some studies were conducted in children. There were 8 clinical trials and 8 cross- sectional studies. In the clinical trials, patients were studied for between 10–28 weeks. Different techniques were used for the measurement of serum vitamin D level, although enzyme-linked immunosorbent assay (ELISA) was the most commonly used technique. The characteristic and chief findings of included studies are summarized in Tables 1 and 2.

Prevalence of VDD and effect of vitamin D on liver function test

These studies demonstrated that there was a high rate of VDD in chronic liver disease (CLD) ranging from 45% - 80.2% [18–20]. In a study performed in 2010, patients with non-cholestatic liver disease had significantly lower vitamin D level [19]. A low serum vitamin D level was seen in cirrhotic patients compared with non-cirrhotic CLD patients [19].

Lorvand et al. using 25 μg/day calcitriol (1000 IU vitamin D) for 12 w and Foroughi et al. with administration 50000 IU/day for 10 w vitamin D per day, reported that both ALT and AST levels were reduced after these periods of supplementation therapy in patients with NAFLD. Although, Foroughi et al. administered higher dose of vitamin D, the reduction in aminotransferases approached significance (p=0.057) [10, 21, 22]. Lorvand et al. showed that administration of vitamin D plus calcium carbonate was more effective in increasing serum vitamin D level [23]. However, Sharifi et al. observed that an intake of 50000 IU vitamin D every two weeks for 4 months resulted in a

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Table 1. Summary of the randomized clinical trials of vitamin D in liver disease.

Ref.	City	Sample size (Drop rate)	Population	Intervention group	Control group	Serum vitamin D (ng/ml)		Technique	Duration	Outcome	
						Before	After			Main	Extra
Lorvand AH, 2017 [21]	Tehran	120 (10)	110 Pts with NAFLD confirmed by US and vit D level <15 ng/ml, BMI: 25–35 kg/m^2, daily Ca intake: 700–800 mg/day, with age of 18–65 y	Group I: 15 F & 22 M pts, received 25 μg/day calcitriol (1000 IU vit D) + placebo for 12 w, with mean age: 39.8±11 y Group II: 14 F & 23 M pts received 25 μg/day calcitriol + 500 mg/day calcium carbonate for 12 w with mean age: 38.3 ±10.1 y	13 F & 23 M pts received placebo + placebo with mean age: 44±10.8 y	Int: Group I: 9.9±0.6 Group II: 9.9±0.6 Ctrl: 10±0.6	Int: Group I: 21.4±0.7 Group II: 27.1±1.1 Ctrl: 11±0.7	ELISA	12 w	↓ in ALT, FPG, grade of fatty liver and ↑ in vit D level and HDL in group I & II compared with placebo*	Change in BMI value between three groups**
Lorvand AH, 2016 [22]	Tehran	80 (7)	73 Pts with NAFLD confirmed by US and vit D level <15 ng/ml, with age of 18–65 y	15 F & 22 M, received hypocaloric diet (< 500 kcal/day) & 1000 IU/day vit D (25 μg/day calcitriol) for 12 w, mean age: 39.8±11 y	13 F & 23 M received hypocaloric diet (<500kcal/day) & placebo, mean age: 44±10.8 y	Int: 9.9±3.9 Ctrl: 10.06±3.8	Int: 27.1±7.2 Ctrl: 11±4.7	ELISA	12 w	Higher ↓ in grade of fatty liver in int. group*. ↓ AST, ALT and HOMA.IR in int. group*. ↑ AST in placebo group*.	↑ HDL in int. group and decrease in placebo group*. Higher ↓ in ALT, TG and HOMA-IR in int. group*
Foroughi M, 2016 [23]	Isfahan	60	60 pts with NAFLD confirmed by US with mean age of 48.5 y	30 pts received 50000 IU/week for 10 w vit D	30 pts received placebo	Int: 19.63±0.4 Ctrl: 47±2	Int: 46.87±5.2 Ctrl: 45.8±0.4	ELISA	10 w	↓ in FBS, insulin and HOMA-IR in int. group*	change in HOMA-B**
Sharifi N, 2016 [24]	Ahvas	60 (7)	53 pts with NAFLD confirmed by US and increased level of ALT, with age of 18–70 y	14 F & 13 M, received 50000 IU/2 weeks for 4 m vit D, with mean age of 40.33±8.6	13 F & 13 M, received placebo, with mean age of 43.92±9.5	Int: F: 10 M: 15.7 Ctrl: F: 18.3 M: 15.4	Int: F: 33.6 M: 30 Ctrl: F: 24.4 M: 17.5	NM	4 m	↓ in TC, LDL, hs-CRP in female* ↑ TC in male* ↓ ALT in female*	↓ BMI in both male and female* ↓ LDL in male** ↑ adiponectin in female*
Foroughi M, 2015 [27]	Isfahan	60	60 pts with NAFLD confirmed by US	30 pts received 50000 IU/week for 10 w vit D	30 pts received placebo	Int: 19.63±0.4 Ctrl: 47±2	Int: 46.87±5.2 Ctrl: 45.8±0.4	ELISA	10 w	↓ grade of fatty liver in int group*	↓ in FBS and insulin resistence*
Foroughi M, 2014 [10]	Isfahan	60	60 pts with NAFLD confirmed by US with mean age of 48.5 y	30 pts received 50000 IU/week for 10 w vit D	30 pts received placebo	Int: 19.63±0.4 Ctrl: 47±2	Int: 46.87±5.2 Ctrl: 45.8±0.4	ELISA	10 w	↓ TG and CRP level in int. group (compare with baseline)* Near significant ↓ in AST and ALT	↓ in CRP level in int. group compare with placebo group**
Sharifi N, 2014 [28]	Ahvas	60 (7)	53 pts with NAFLD confirmed by US and increased level of ALT, with age of 18–70 y	14 F & 13 M, received 50000 IU/2 weeks for 4 m vit D, with mean age of 40.33±8.6 y	13 F & 13 M, received placebo, with mean age of 43.92±9.5	Int: 11.5 Ctrl: 16.85	Int: 30 Ctrl: 19.20	NM	4 m	↓ TNF-α and MDA in int. group** near significant ↓ in hs-CRP level ↓ FBS, fasting insulin level, HOMA-IR, TNF-α and TGF-β in int. group** ↓ AST and ALT in both group**	changes in grade of fatty liver in both group** difference in reduction of BMI in both groups**
Najarzadeh A, 2013 [25]	Isfahan	80 (7)	NAFLD pts with VDD + BMI>25 kg/m^2 + ↑ALT, with age of 25–65 y	10 F & 27 M, received hypocaloric diet and 50000 IU/w for 12 w vit D, with mean age of 43.7±9.2 y	8 F & 28 M, received hypocaloric diet and placebo, with mean age of 44.7±10.6 y	NM	NM	HPLC	12 w	↓ AST, ALT, ALP in int. group (compared with placebo)* ↓ grade of fatty liver in int. group*	↓ BMI and WC in int group (compared with placebo)*

Pts: patients, F: female, M: male, IU: international unit, NAFLD: non-alcoholic fatty liver disease, vit D: vitamin D, VDD: vitamin D deficiency, US: ultrasonography, Ca: calcium, Int: intervention, Ctrl: control, ELISA: enzyme-linked immunosorbent assay, ALT: Aspartate Aminotransferase, AST: Alanine Aminotransferase, FPG: fasting plasma glucose, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, TC: total cholesterol, BMI: Body mass index, HOMA-IR: Homeostatic model assessment-insulin resistance, hs-CRP: high sensitivity c-reactive protein, FBS: fasting blood sugar, NM: not mentioned, TNF-α: tumor necrosis factor- α, MDA: malondialdehyde, HPLC: High-performance liquid chromatography, WC: waist circumference, NAFLD: Nonalcoholic fatty liver disease.

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Table 2. Summary of cross sectional studies of vitamin D in liver disease.

Ref.	City	Sample size	Population	Technique	outcome	
					Main	Extra
Yazdanpanah K, 2017 [26]	Sanandaj	90	35 F & 55 M Pts with hepatic cirrhosis	chemiluminiscence	Positive association between cirrhosis severity and vit D level* Highest vit D level was in autoimmune hepatitis Normal ALT and AST pts had higher vit D	–
Zolfaghari H, 2016 [59]	Isfahan	317	Group1: 91 F & 68 M NAFLD pts with a mean age of 47.8±9.2 y Group2: 90 F & 68 M healthy subjects with a mean age of 48±9.1	NM	Significantly higher vit D level in group2	–
Mohamad khani A, 2015 [60]	Tehran	173	55 F & 118 M pts with HBV chronic hepatitis with a mean age of 37±9.7 y	ELISA	42% pts had vit D lower than normal	Positive association between vid D and miR-378* Reversely association between vit D and viral load*
Hajiabbasi A, 2015 [18]	Rasht	97	45 F & 55 M Pts with cirrhosis with a mean age of 51±13 y	ELISA	80.2% had VDD.	Association between cirrhosis and vit D, C, p, ALP, PTH and FBS**
Hashemi kani A, 2013 [61]	Tehran	200	Group1: 62 F & 38 M pts with NAFLD with a mean age 37.9±6.9 y Group2: 58 F & 42 M healthy subject with a mean age of 37.9±6.9 y	NM	↓ vit D between groups. Vit D dietary intake is lower in group1	–
Mohammadi B, 2012 [20]	Tehran	48	21 F & 27 M children Pts with cholestatic liver disease with a mean age of 299±676.8 day	NM	45% had VDD.	Association between children with or without rickets**
Movassaghi Sh, 2012 [62]	Tehran	23	23 pts underwent liver transplant with a mean age of 40.2±10.9 y	NM	Vit D level was lower in liver transplant recipients than heart transplant patient**	–
Miroliaee A, 2010 [19]	Tehran	130	Group1a: 17 F & 22 M non-cirrhotic with a mean age of 43.52 ±13.7 y Group1b: 23 F & 28 M cirrhotic with a mean age of 41.26±12.2 y Group2: 16 F & 24 M healthy subjects with a mean age of 49.98±9.29 y	RIA	VDD in group1: 51.1% Lower vit D in group1* Lower vit D in cirrhotic group than non-cirrhotic	Higher INR and bilirubin in VDD pts*

pts : patients, F: female, M: male, IU: international unit, Vit D: vitamin D, VDD: vitamin D deficiency ALT: Aspartate Aminotransferase, AST: Alanine Aminotransferase, FBS: fasting blood sugar, miR: microRNA, ELISA: enzyme-linked immunosorbent assay, PTH: parathyroid hormone, ALP: alkaline phosphatase, NAFLD: Nonalcoholic fatty liver disease, NM: not mentioned
*: significant, **: not significant

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non-significant reduction in aminotransferases, but there was a gender difference; a significant reduction in female patients but not in men [24]. Consistent with these results, Najarzadeh et al. had demonstrated that administration of hypocaloric diet plus 50000 IU vitamin D per week for 12 week leads to significant decrease in AST and ALT levels [25]. In a study conducted on patients with non-cholestatic CLD, patients with VDD had significantly higher levels of bilirubin and International normalized ratio (INR) [19]. It was also observed that cirrhotic patients with normal AST and ALT values had a higher vitamin D level [26].

Effect of vitamin D on grade of fatty liver, lipid profile, glucose metabolism and other markers or conditions

Various doses of vitamin D have been used in randomized control trials (RCTs). In two RCT studies which used the same dose of vitamin D supplement by Lorvand et al. there was a significant reduction in the grade of fatty liver in patients with NAFLD [21, 22]. Similarly, Foroughi et al. and Najarzadeh et al. investigated the effects of administering 50000 IU vitamin D but with small difference in follow up period time (12 w vs. 10 w respectively) found that giving vitamin D supplement in patients with NAFLD resulted in reduced grade of fatty liver [25, 27]. In contrast with these results, Sharifi and colleagues concluded that administration of lower doses of vitamin D (50000 IU vitamin D every 2 week) for 4 months led to a non-significant reduction in grade of fatty liver disease [28]. Yousefi et al. investigated 164 patients with chronic hepatitis C virus and reported that there was an insignificant association between incidence of fatty liver and vitamin D level [29]. Yazdanpanah et al. observed positive and significant association between vitamin D level and cirrhosis severity in their cross-sectional study [26]. However, Hajiabbasi and colleagues found no significant association between cirrhosis and vitamin D status [18].

The effect of vitamin D on lipid profile was evaluated in four clinical trials. All four studies showed beneficial effects of vitamin D supplementation on lipid profile in patients with NAFLD which could be secondary influence on severity of fatty liver [10, 21, 22, 24]. In 2017 and 2016, Lorvand and his colleagues found that administration of vitamin D supplement at a dose of 1000 IU/day with or without calcium resulted in an increase in serum high density lipoprotein (HDL) levels without significant changes in other parameters of the lipid profile [21, 22]. Foroughi et al. with weekly administration 50000 IU vitamin D found significant reduction in serum triglycerides (TG) [10]. Also Sharifi et al. in their RCT study observed that an intake of 50000 IU vitamin D every 2 weeks could lead to significant reductions in total cholesterol and low density lipoprotein (LDL) in women but significant increase in total cholesterol in men [24]. In this study, LDL level of male gender in intervention group was decreased but it was not significant [24].

The effects of vitamin D on glucose metabolism in patients with liver disease were also examined in several RCT studies. There was a significant difference in fasting blood glucose (FBG) and the homeostatic model assessment-insulin resistance (HOMA-IR) between patients with NAFLD receiving vitamin D supplement or a placebo, with a significant reduction in FBG and HOMA-IR in the intervention group [21–23, 27, 28]. However, no significant decrease in Homeostatic model assessment-beta cell (HOMA-B) was found [23].

Four studies have investigated the association between vitamin D on body mass index (BMI) and waist circumference (WC). In this regard, 2 studies found that giving 50000 IU vitamin D every 2 w for 4 months, and giving 50000 IU vitamin D every week for 12 weeks was associated with a significant reduction in BMI and WC [24, 25]. However, Sharifi et al. and Lorvand et al. could not establish this beneficial effect of vitamin D supplementation therapy on BMI [21, 28].

Vitamin D treatment has been reported to be effective in controlling inflammatory status. These effects were demonstrated in the studies of Sharifi and Foroughi and administration of vitamin D resulted in decrease in serum high sensitivity C-reactive protein (hs-CRP) level in patients with NAFLD [10, 24, 28]. Although, the reduction, shown in Sharifi's study was near significant for the whole group, a significant effect was observed in the women, with respect to a reduction in serum hs-CRP [24].

Characteristics of the studies in the field of renal disease

Vitamin D status has been evaluated in patients with kidney disease in several cities in Iran. Tehran and Isfahan are the two cities that have the most studies in this field. Three different population samples have been assessed in these studies: (i) hemodialysis (HD) patients, (ii) peritoneal dialysis (PD) patients and (iii) kidney transplanted patients. Most of these studies (twelve studies) were conducted in patients on hemodialysis (HD). The mean age of all patients evaluated in these studies was approximately 46 years. These studies include 6 clinical trials, 14 cross- sectional and 2 cohort studies. The follow up period in clinical trials are different, ranging between 2 and 12 months. Various methods were used for measuring serum vitamin although ELISA was the most common technique used. The characteristic and chief findings of the included studies are summarized in Tables 3 and 4.

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Table 3. Summary of randomized clinical trial studies associated with vitamin D and kidney diseases.

Ref.	City	Sample size (drop rate)	Population	Intervention group	Control group	Serum Vitamin D (ng/ml)		Technique	Duration	Outcome	
						Before	After			Main	Extra
Jalalzadeh M, 2017 [35]	Tehran-Zanjan	113	46 F & 57 M undergoing HD pts with VDD and mean age of 56.25±12.6 y	26 F & 31 M of HD pts with VDD, received 300000 IU vit D/IM at the beginning and after 2 m	20 F & 36 M of HD pts with VDD received placebo	13.85±6.5	48.5±20.7	RIA	4 m	87.8% of total pts had VDD. 71.5% of VDD pts and 40% of normal vit D level had sHPT.	↓ in iPTH, ALP and Ca* ↑ serum albumin*
Naini AE, 2016 [37]	Isfahan	64	HD pts with VDD	16 F & 16 M of HD pts, received 50000 IU vit D/week for 12 w and then every three weeks (total: 650000 IU) with mean age of 60±19 y	16 F & 16 M HD pts are received placebo with mean age 62±21y	M: 22.12±7.72 F: 20.04±8.52	M: 79.24±7.59 F: 79±9.41	NM	4 m	↑ in adiponectin *↓ in leptin level*	-
Naini AE, 2015 [38]	Isfahan	64	Anemic HD pts with VDD	16 F & 16 M of HD pts received 50000 IU vit D/week for 12 w and then every three weeks (total: 650000 IU)	16 F & 16 M HD pts are received placebo	M: 22.12±7.72 F: 20.04±8.52	M: 79.24±7.59 F: 79±9.41	NM	4 m	Association between vit D level and require dose of EPO*	Association between Hb and vit D level** Association between BMI and vit D level**
Haghighi A, 2013 [40]	Tehran	53	53 osteoporptic postmenopausal women with normal renal US and no history of renal stone and smoking, and mean age of 55.57±11.09 y	53 osteoporptic postmenopausal women received 1000 mg Ca + 400 IU vit D/day	-	NM	NM	NM	12 m	1.9% developed nephrolithiasis. No significant difference between urine and serum calcium in both group	-
Bonakdaran SH, 2008 [14]	Mashhad	32 (5)	13 F & 14 M undergoing HD	6 F & 7 M HD pts with mean age of 48 ±16.3 y, received 0.5 µg/day oral calcitriol for 8 w	7 F & 7 M HD pts with mean age of 51.5±19.8 y, received placebo	NM	NM	NM	8 w	↓ in HbA1C, HOMA-IR, total cholesterol and TG in int. group*	↓ FBS and LDL and ↑ in HDL in int group**
Khajehdehi P, 1999 [63]	Shiraz	84 (19)	65 HD pts without using lipid-lowering drugs and with mean age of 31.4 y	Group I: 15 HD pts received 50000 IU/day vit D Group II: 15 HD pts received 200 mg/day vit C Group III: 21 HD pts received 200 mg/day vit E	14 HD pts received placebo	NM	NM	NM	3 m	↓ TG in group I* ↓ LDL and TC in group II* ↑ HDL in group III*	No remarkable side effects were seen

F: female, M: male, pts: patients, IU: international unit, IM: intramuscular, int: intervention, HD: haemodialysis, Vit D: vitamin D, Vit C: vitamin C, Vit E: vitamin E, VDD: vitamin D deficiency, Hb: haemoglobin, HbA1c: haemoglobin A1c, Ca: calcium, FBS: fasting blood sugar, ALP: alkaline phosphatase, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, BMI: body mass index, sHPT: secondary hyperparathyroidism, iPTH: intact parathyroid hormone, EPO: erythropoietin, HOMA-IR: Homeostatic model assessment-insulin resistance, RIA: radioimmunoassay
NM: not mentioned, *Significant, **not significant

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Table 4. Summary of the cross-sectional and cohort studies associated with vitamin D in kidney disease.

Ref	City	Sample size (drop rate)	Population	Technique	outcome	
					Main	Extra
Mortazavi ZS, 2017 [36]	Isfahan	98 (17)	40 F & 41 M pts undergoing PD, including 36 pts with GSQ and mean age: 50.7±16.6 y and 45 pts with PSQ and mean age: 56.8±13.4 y	HPLC	61.1% of GSQ and 75.6% of PSQ had VDD (69.1% of all pts)	Reverse association between vit D level and PSQ*
Balouche A, 2017 [64]	Zabol	60	32 F and 28 M pts undergoing HD with mean age of 48.13±17.35 y	NM	Mean vit D level in pts with and without renal osteodystrophy was 22 ng/ml and 25 ng/ml*	80% had renal osteodystrophy
Jalali Gh, 2017 [15]	Mashhad	86	38 F & 48 M pts underwent kidney transplant with a age of >18 y and with using NCEP ATP III criteria divided into two group: Pts with MS (18 F & 25 M, 50%) with mean age of 40.16±11.3 y and pts without MS (20 F & 23 M, 50%) with mean age of 32.47±11.8 y	RIA	Prevalence of VDD and MS: 81.4% & 50% Higher BMI in MS group* Lower vit D level in female in MS group* Higher TG level and WC in MS group*	Higher HDL and lower FBS in without MS group** Difference in BP between two groups**
Ahmadi F, 2016 [3]	Tehran	145	62 F & 83 M Pts undergoing HD, mean age: 58.2±16 y	ELISA	71% had low vit D	VDD associated with increased risk of MS**
Mirchi A, 2016 [34]	Qom	208	176 pts undergoing HD, mean age: 52.4 ±15.9 y 32 pts undergoing PD, mean age: 61.6±15.8 y	ELISA	92.5% of HD pts & 96.9% of PD pts had low vit D	Association between vit D level and age, quality and duration of dialysis** Inverse association between 25(OH)D and hs-CRP and NLR in haemodialysis patients*
Nazemian SS, 2016 [44]	Mashhad	96	51 F & 45 M pts underwent kidney transplantation without using vitamin D or calcium supplement consumption during the past 6 months, with mean age of 41 y	NM	78.1% had vit D lower than normal	changes in mean of vit D level in winter and summer**
Farhadnejad H, 2016 [43]	Tehran	1699 (Cohort)	863 F and 836 M participants from general population without CKD at baseline, with mean age of 43.3±11.4 y. Dietary intake of vitamins were evaluated and participants were followed for mean of 3.6 y	NM	Pts affected by CKD were more female Higher intake of vit D correlated with reduced risk of CKD (OR 0.39; 95% CI 0.21–0.7)	Higher intake of vit B9, B12, C and E are also associated with decreased risk of CKD*
Saber A, 2015 [41]	Tehran	82 (Cohort)	37 F & 35 M CMV negative pts underwent kidney transplantation. Vit D before transplantation was measured and pts followed for 4 m. At the end, pts divided into two groups: CMV positive and CMV negative	NM	Vit D before transplantation and at the end was not significantly differed between two groups	Vit D decrease in CMV positive pts and increase in CMV negative pts*
Zahed N, 2014 [65]	Tehran	135	66 F & 69 M pts undergoing HD with age of ≥15 y and 59 (44%) had diabetes	NM	63% had low and 5% had toxic level of vit D	Association between 25-(OH)D level and muscle force*
Atapour A, 2013 [30]	Isfahan	90	34 F & 56 M Pts undergoing HD, mean age:36±11.4 y	Radio competitive	63.9% F and 32.7% M had low vit D (44.4% of all pts)	Male pts had lower calcium and Phosphate and female pts had lower ALP and PTH level

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Table 4. (Continued)

Ref	City	Sample size (drop rate)	Population	Technique	outcome	
					Main	Extra
Savaj S, 2012 [39]	Tehran	113	58 F and 55 M pts underwent kidney transplant with mean age of 46.1±13.6 y	chemilumi-nescence	45% had VDD, 49.5% had insufficiency, 76.2% had Hyperparatyroidism and 58% had osteoporosis	Association between vit D deficiency and high parathyroid hormone and serum creatinine*
Derakhshan A, 2011 [32]	Shiraz	82 (25)	30 F and 27 M pts underwent kidney transplant with mean age of 18.7±4.25 y	RIA	VDD: 7%, HPT: 47.3%	Hypophosphatemia: 8.8% hyperphosphatemia: 15.8% hypercalcemia: 47.3% hypocalcemia: 0%
Nasri H, 2007 [42]	Shahrekord	36	15 F & 21 M pts undergoing HD, with mean age: 47±17 y and mean vit D level: 10.5±18.7 nmol/L	ELISA	Positive association between vit D and H.pylori IgG antibody titer*	vitamin D supplement may control the inflammatory status in HD pts
Mojerloo M, 2012 [31]	Gorgan	98	Group1: 31 F & 18 M pts underwent kidney transplant, with mean age of 35.59±10.4 y Group2: 45 F & 4 M healthy subjects with mean age of 35.06±13.4 y	ELISA	Vit D lower than normal in group1 and 2 was 98% (55.1% VDD) and 65.3 (2% VDD).	Different BMI between two groups**
Taziki O, 2011 [33]	Sari	92	Group1: 31 F & 15 M pts underwent kideney transplant with mean age of 41 ±14.2 y Group2: 31 F & 15 M healthy subjects from pts' relatives with mean age of 41.4±13.7 y	ELISA	Vit D lower than normal in group1 and 2 was 93.5% (34.8% VDD) and 89.1% (26% VDD).	-
Valizadeh Sh, 2014 [66]	Tabriz	89	Group1: 18 F & 28 M HD pts with mean age of 60.3±14.5 y Group2: 23 F & 20 M healthy subjects with mean age of 54.6±17.8 y	ELISA	↓ vit D in group1 ↓ vit D in female in group1	No significant association between vit D and fetuin-A protein

F: female, M: male, pts: patients, HD: haemodialysis, PD: peritoneal dialysis, vit D: vitamin D, VDD: vitamin D deficiency, CKD: chronic kidney disease, FBS: fasting blood sugar, BMI: body mass index, TG: triglyceride, WC: waist circumference, GSQ: good sleep quality, PSQ: poor sleep quality, MS: metabolic syndrome, CMV: cytomegalovirus, HPT: hyperparathyroidism, PTH: parathyroid hormone, ELISA: enzyme-linked immunosorbent assay, HPLC: High-performance liquid chromatography, RIA: radioimmunoassay
NM: not mentioned, *Significant, **not significant

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Prevalence of insufficiency and deficiency of vitamin D

A review of the included studies showed a high rate of VDD and insufficiency in almost all studies. The prevalence of lower than normal serum vitamin D in studies performed in our region varied from 44.4 in Isfahan to 98% in Gorgan [30, 31], whilst the prevalence of VDD was between 7% in Shiraz and 87.8% in Tehran in patients with renal disease [34, 35]. The mean age of patients in the Shiraz study was 18.7±4.25 years [32]. Apart from the Shiraz study that was conducted in young patients with renal disease, the lowest prevalence of VDD, in other studies which were similar in term of age, was 34.8% in Sari [33]. In one study that compared the level of serum vitamin D in HD with peritoneal dialysis (PD) patients, a high prevalence of vitamin D insufficiency was found in the PD patients [34]. Among patients undergoing HD, PD and kidney transplant patients, the reported prevalence of VDD were 87.8%, 69.1% and 81.4%, respectively [15, 35, 36].

Effect of vitamin D on serum biochemical markers or clinical conditions

Blood glucose and lipid profile

The dose of vitamin D supplements administered to patients was different in most of RCTs. In one RCT study, different from other RCTs, used a very low dose vitamin D (0.5 μg calcitriol/day orally), no significant reduction in fasting blood glucose (FBG) but a significant decrease in HOMA-IR and HbA1c level were found, respectively [14]. Administration of 650000 IU vitamin D in a divided dose was associated with a significant increase in serum adiponectin and reduction in serum leptin level in HD patients [37].

In another RCT lipid profile after administration 0.5 μg of calcitriol per day orally, the level of TG and cholesterol were significantly decreased although the increase in serum HDL was not significant compare to the placebo group [14].

Hemoglobin and acute phase reactant protein

A RCT in Isfahan showed that there was an association between vitamin D status and the requirement for erythropoietin in dialysis patients, so that weekly supplementation with 50000 IU of vitamin D for 12 w could significantly reduce the required dose of erythropoietin (EPO) [38]. In spite of this, no significant association was observed between hemoglobin levels in these patients and level of vitamin D [38]. The role of vitamin D in inflammatory status in dialysis patients has been assessed. Mirchi et al. reported that vitamin D level was significantly associated with serum hs-CRP and neutrophil-lymphocyte ratio as a marker of inflammation [34].

Bone metabolism

Savaj et al. reported that vitamin D deficiency was significantly related to higher levels of PTH and creatinine [39]. Consistent with this result, Jalalzadeh et al. observed that an intramuscular injection of 300000 IU vitamin D initially and after 2 months resulted in a significant reduction in PTH, serum calcium and ALP [35]. Two studies were performed in Tehran including 293 patients, there was significant association between lower than normal level of vitamin D and hyperparathyroidism [35, 39]. Bonakdaran et al. observed a near significant reduction in PTH in patients taking 0.5 μg calcitriol per day [14].

Haghighi et al. aimed to determine the risk of stone formation with oral intake of calcium and vitamin D supplementation followed osteoporotic female using 1000 mg calcium plus 400 IU vitamin D per day for 1 year [40]. They did not find a significant difference between urine and serum calcium in their participants and rate of developing nephrolithiasis was 1.9% per year.

Bacterial and viral infections

A cohort study in patients undergoing renal transplantation with using immunosuppressive drugs revealed that vitamin D levels decreased in patients with CMV, while it increased in CMV negative patients [41]. This showed that any significant correlation between vitamin D levels and CMV infection was not found during follow-up period after kidney transplantation but it was observed that, compared with the time before transplantation. Also, in this regard, Nasri et al. observed that the titers of Helicobacter pylori IgG antibody were significantly and positively related with serum vitamin D level [42].

Further clinical findings

Farhadnejad et al. in 2016, showed that a higher dietary intake of vitamins, including vitamin D, significantly reduced the risk of CKD [43].

Except for one study, none of included studies evaluated the effect of seasonal change in vitamin D level. Nazemian et al. reported that the mean value of vitamin D level had not significantly changed between summer and winter [44].

Vitamin D has also been related to effects on sleep quality in dialysis patients and muscle strength [38, 40].

Discussion

Epidemiological studies show that insufficiency of vitamin D is associated with NAFLD [45], and a meta-analysis has shown a 26% higher risk of NAFLD in Vitamin D deficient patients [46]. The grade of fatty liver in NAFLD was found to be inversely associated with serum vitamin D level [22]. Vitamin D deficiency is prevalent (45–80%) in patients

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with chronic liver disease in Iran [18, 20]. There are little data regarding the effects of hypovitaminosis D and vitamin D supplementation on liver enzymes. Several cross-sectional studies reported a significant correlation between low vitamin D level and high serum aminotransferases [47, 48]. Although in two recent clinical trials administration of vitamin D supplement revealed no significant decrease in aminotransferases [10, 24]. However, another study found that vitamin D supplementation may result in significant reduction in AST and ALT level [22]. For elucidation the effect, further studies with larger sample size, stronger design and considering confounding factors are needed.

Observational studies have reported adverse effects of low vitamin D level on lipid profile [49]. Results of meta-analysis based on 12 RCTs, showed that vitamin D (calcitriol or Cholecalciferol) administration significantly increased LDL with no significant effect on HDL, TG and total cholesterol (TC) [50]. However, a recent meta-analysis consisting of 17 RCTs demonstrated statistically significant reduction in TG level and increase in LDL level with vitamin D supplementation therapy. In 3 clinical trials performed in Iran, vitamin D supplementation therapy resulted in beneficial changes in lipid profile apart for one study total cholesterol significantly increased after administration vitamin D, but only in men [10, 22, 24].

Vitamin D insufficiency and deficiency are common in patients with chronic kidney disease (CKD) [51]. Vitamin D insufficiency and deficiency are prevalent among dialysis patients and estimated to be up to 98% and 87.8%, respectively and this is consistent with prevalence in several studies conducted in the world that was reported 80–97% [51, 52]. However many studies have reported a lower prevalence [35]. A number of studies evaluated the effect of vitamin D supplementation on serum PTH, calcium and phosphorous in patients with CKD [53, 54]. Although in one study included in this review serum calcium was significantly decreased with vitamin D supplementation but in two another studies calcium was significantly increased. In two of the three clinical trials evaluated these parameters, significant and near significant association with vitamin D supplementation and PTH reduction was observed. Results of other clinical trials was similar with this finding [53, 55, 56] and therefore vitamin D administration could be beneficial in treating secondary hyperparathyroidism and also preventing renal osteodystrophy.

An abnormal lipid profile may exacerbate atherosclerosis in dialysis patients, but, the effect of vitamin D supplementation on lipid profile is still controversial. In two clinical trials evaluated this effect, vitamin D therapy significantly reduced TG level after 2–3 months vitamin D therapy, but LDL and HDL did not changed significantly. Findings obtained by Yeksan et al. [57] and Lin et al. [58] confirm these results.

Strengths and limitations

This review which has evaluated clinical trials, observational and cohort studies conducted in the field of vitamin D status and supplementation in patients with liver or renal disease in Iran. A major limitation of present study is the variation between the methodological issues addressed in different studies. Different studies have used various cut offs for vitamin D status which make them difficult to draw a conclusion.

Conclusion

Our systematic review showed that vitamin D deficiency is prevalent in patients with chronic liver or kidney disease in Iran. This study also showed different beneficial effects of a normal level of vitamin D level or vitamin D following supplementation therapy, in different parameters including: glucose homeostasis, liver function test, lipid profile, grade of fatty liver and bone mineral homeostasis in vitamin D deficient patients with various liver or kidney disease. The effect of vitamin D supplementation on serum aminotransferases of patients with liver disease is controversial in Iranian studies. Also, the effect of vitamin D supplementation on lipid profile such as TG and HDL is controversial and needs further research. Regarding to these controversial findings, conducting additional studies with the same protocol and dose of vitamin D administration appears to be necessary for any substantive conclusions of these effects.

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Conflicts of interests
No conflicts of interest exist.

Authors' contributions
All authors contributed to the conception and design of the study. SMP and RJE collected the all references in the field according to the databases and wrote the first draft of manuscript. MR, AA, HGH, ME, RS, GAF and MGM rechecked and interpreted the references and obtained data. All authors revised the manuscript critically for important intellectual content and read and approved the final manuscript.

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