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Review

Vitamin D Supplementation for Steatotic Liver Disease: an Updated Systematic Review and Dose-Response Meta-analysis of Randomized and Nonrandomized Interventional Studies

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A B S T R A C T

Metabolic dysfunction-associated steatotic liver disease (MASLD) is among the leading causes of chronic liver disease, with few approved treatment options. Vitamin D supplementation has been proposed as a safe and efficacious supplement intervention for MASLD. The current study aimed to systematically evaluate the effect of vitamin D supplementation in any preparation on hepatic (histological, radiological, and biomarker) and metabolic parameters (glucose regulation, lipid profile, and indices of obesity) in patients diagnosed with steatotic liver disease. These effects were compared with patient baseline and/or placebo response, where available. MEDLINE, Scopus, Web of Science, the Cochrane Library, clinicaltrials.gov, and International Clinical Trials Registry Platform were systematically searched for relevant randomized or nonrandomized studies of intervention. Screening and data extraction were completed by independent pairs of reviewers. Effects were pooled using random-effects meta-analyses. One-stage dose–response analysis was performed for alanine aminotransferase (ALT) and γ-glutamyl transferase. The effect of baseline vitamin D, ALT, body mass index, and vitamin D response on treatment response was explored via metaregression. Treatment efficacy was evaluated in subgroup analyses according to patient and intervention characteristics. A total of 28 studies (21 randomized controlled trials) were analyzed. Statistically significant improvements were noted in FibroScan parameters, liver enzymes, insulin resistance, serum triglyceride, and high-density lipoprotein. However, the magnitude of effect regarding these improvements was smaller than thresholds for clinical benefit, and analyses demonstrated inconsistencies. Subgroup analyses failed to identify a specific subset of patients with MASLD benefiting from supplementation. Vitamin D supplementation was safe and well-tolerated, but no meaningful clinical benefit was identified for hepatic or metabolic parameters of interest in MASLD.

This trial was registered at PROSPERO as CRD420251125809.

Keywords: MASLD, NAFLD, vitamin D, dose-response meta-analysis, systematic review

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; APRI, AST-to-platelet ratio; BF%, body fat percentage; CAP, controlled attenuation parameter; CI, confidence interval; CK-18, cytokeratin-18; FIB-4, fibrosis-4; FPG, fasting plasma glucose; FLI, fatty liver index; GGT, gamma-glutamyl transferase; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MD, mean difference; MSALD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NAS, NAFLD activity score; RCT, randomized controlled trial; ROB, risk of bias; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio.

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Introduction

Steatotic liver disease is a leading cause of chronic liver disease and hepatic failure worldwide—affecting an excess of a third of the adult population in certain geographic regions [1,2]. Metabolic disorders—chiefly obesity and glucose dysregulation—are major contributors to the pathophysiology underlying metabolic dysfunction-associated steatotic liver disease (MASLD) on the individual level, and its epidemic on a population level [3,4]. The upward trend in the prevalence of these comorbidities has further positioned MASLD to become the most important etiology for chronic liver disease [5].

Few effective interventions have been identified for MASLD. Control of concomitant metabolic disorders, along with dietary and lifestyle adjustments, has been the mainstay of treatment. In contrast, only recently have pharmacological treatments been approved for specific use in patients with MASLD [6,7]. Dietary supplements have also been widely explored as a potential strategy in MASLD treatment [8]. Their availability and the perceived positive patient attitudes toward supplement use—possibly promoting treatment adherence—have increased the popularity of these approaches as adjuvant treatments for metabolic disorders [9,10]. Among dietary supplements, vitamin D has been proposed as a potential candidate for the treatment MASLD—particularly among vitamin D-deficient patients [11–13].

Evidence on the possible role of vitamin D deficiency in MASLD pathophysiology has been controversial. Earlier observational studies had suggested an association between vitamin D deficiency and MASLD prevalence [14]. Although studies have failed to identify a causative role for vitamin D deficiency in MASLD via Mendelian randomization [15,16], or a link between vitamin D deficiency and pathological severity of disease [17]. However, several interventional studies have demonstrated some improvement in hepatic outcomes following vitamin D supplementation among patients with MASLD [11–13]. Systematic appraisal of the available interventional evidence has also suggested some possible metabolic benefits for vitamin D supplementation in deficient individuals, which may in turn improve MASLD outcomes in patients [18,19].

The current review aimed to systematically evaluate and quantitatively synthesize the evidence from interventional studies focusing on vitamin D supplementation in adult patients with steatotic liver disease [a diagnosis of MASLD, or an equivalent diagnosis under outdated nomenclature i.e. MAFLD or nonalcoholic fatty liver disease (NAFLD)] by updating previous reviews on the topic and attempting to overcome certain analytical limitation in these reviews—chiefly a lack of consideration for the quality of evidence including inconsistencies or imprecision noted in the findings of primary studies; no evaluation crucial information on efficacy regarding histological and radiological endpoints (partially due to exclusion of nonrandomized studies); and lack of a robust and detailed examination of trial or patient characteristics associated with treatment response and the magnitude of effect (compared with a threshold of clinical significance)—leading to an unwarranted and overoptimistic reliance on findings of "statistically significant" benefits [20,21]. We examined the effect of vitamin D supplementation (regardless of preparation) on hepatic (histological, radiological, and biomarker) and metabolic (glucose regulation, lipid profile, and indices of obesity) outcomes in MASLD populations. In addition to results from randomized placebo-controlled trials (RCTs), evidence from qu asi-experimental studies was also evaluated independently—to evaluate intervention effects compared with baseline. This choice was based on guidance from Grading of Recommendations Assessment, Development and Evaluation (GRADE) on inclusion of evidence from nonrandomized studies where information on "patient important outcomes" (histological and radiological evidence of hepatic response in our case) is missing or sparse in randomized studies, or when randomized studies are deemed to provide a low quality of evidence and nonrandomized studies may "provide higher certainty of evidence" [22]. Dose–response effect was explored, given the broad range of evaluated daily dose equivalents of vitamin D in MASLD. We further attempted to determine if certain patient characteristics, such as patient BMI, baseline vitamin D concentrations, or severity of disease, affect treatment response to better delineate the target population likely to benefit from vitamin D supplementation.

Methods

The current review aimed to synthesize the available evidence regarding the safety and efficacy of vitamin D supplementation in adults with steatotic liver disease. The review protocol has been registered in the PROSPERO (CRD420251125809). Reporting of the review adheres to guidance from the PRISMA (Additional file 1) [23].

Selection criteria

Adults diagnosed with steatotic liver disease fulfilling conventionally acceptable criteria for NAFLD, nonalcoholic steatohepatitis, MASLD, or metabolic dysfunction-associated steatohepatitis (MASH) were the target population for the review (population). Although most studies may have enrolled patients according to older criteria (NAFLD), we will use the updated terminology (MASLD) in the review—given a large overlap between the populations diagnosed with the different criteria and the focus on metabolic outcomes [24]. Vitamin D supplementation, regardless of preparation, dose, and duration, was an eligible intervention (intervention). All these factors were considered evidence synthesis post hoc (sensitivity and subgroup analyses, assessment of indirectness of evidence, and narrative synthesis). Both single-arm before–after studies and randomized placebo-controlled trials were included (comparators and study design). Additional interventions outside of vitamin D supplementation and usual care (lifestyle interventions) were deemed ineligible. Primary outcomes included measures of hepatic function including: histological activity [NAFLD activity score (NAS)], fibrosis, and steatosis scores; radiological measures of hepatic steatosis or fibrosis; liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and alkaline phosphatase (ALP)]; total bilirubin; biomarkers [cytokeratin-18 (CK-18) M30 and M65, N-terminal type III collagen propeptide, and enhanced liver fibrosis test]; and disease activity indices [fibrosis-4 (FIB-4), AST-to-platelet ratio (APRI), fatty liver index (FLI), and NAFLD fibrosis score (NFS)]. Secondary outcomes included anthropometric and metabolic indicators along with other related paraclinical measures: body

weight, BMI, waist circumference (WC), waist-to-hip ratio (WHR), and body fat percentage (BF%); measures of glucose tolerance such as fasting plasma glucose, fasting insulin, hemoglobin A1c, and HOMA-IR; lipid parameters [triglycerides (TG), total cholesterol (TC), LDL, and HDL]. Additional outcomes included changes in serum calcium (Ca), vitamin D, and the total number of participants discontinuing the intervention for any cause (outcomes).

Search strategy

Sources for information included MEDLINE (via PubMed), Scopus, Web of Science, the Cochrane Library, clinicaltrials.gov, and the International Clinical Trials Registry Platform. Each of these was systematically searched for possibly relevant records until the end of June 2025. Keywords derived from MeSH (medical subject heading) entry terms for the target condition, intervention, and outcome were used. Search queries used for each platform are provided in the supplementary material (Supplemental Table 1).

Screening and data extraction

Screening and data extraction were performed for each record by pairs of independent reviewers (TE, SE, FJ, and NB). Conflicts were resolved by consensus or consultation of an independent team member. Records' abstracts were screened against the outlined inclusion criteria following deduplication. Full-text screening was performed for abstracts deemed eligible or those subject to reviewer dispute. For each eligible record, data regarding study design (inclusion criteria, comparator, allocation, and outcomes), population characteristics (demographic data, baseline BMI, vitamin D, and serum ALT), intervention details (form, route, duration, and dose), and outcome measures were extracted by independent pairs of reviewers. Mean difference (MD) from baseline and compared with the control was used as the summary effect measure for all outcomes. MDs were calculated using mean, SD, and the number of participants for the outcome reported in each included record. When necessary, other summary measures [e.g., median with range or IQR; or mean and confidence intervals (CIs)] were converted to mean and SD via conventional conversions [25].

Evidence synthesis

Study and population characteristics were tabulated along with reported safety concerns. Considering interstudy differences, random-effects meta-analyses using the restricted maximum likelihood heterogeneity estimator were performed to pool effect measures for each outcome evaluated in ≥3 studies. I^2 and τ^2 statistics were reported as measures of statistical heterogeneity. Separate meta-analyses were conducted for changes from baseline—using data from all vitamin D arms from controlled or single-arm studies—and change compared with control. Changes in liver stiffness measurement (LSM) were compared with 30% reduction from baseline as a prespecified threshold of clinical significance. Changes in serum ALT were considered clinically significant when a reduction ≥17 IU/L was noted. These thresholds for clinical significance were derived from guidance on monitoring of response to Resmetirom (1 of the only 2 pharmaceutical interventions approved for MASLD)—themselves based on evidence from high-quality RCTs quantifying the threshold of change in noninvasive markers corresponding to improvements in histological outcomes [26]. Multiplicity was addressed via splitting shared comparator groups in multiarm studies. Splitting nominally assigns a portion (e.g., half in the case of 2 intervention arms) of the control group to each intervention arm to avoid unit-of-analysis errors. One-stage dose–response meta-analysis was conducted for changes in serum ALT and GGT using calculated mean daily doses of vitamin D (IU) in trials enrolling participants with vitamin D insufficiency. Model fit was evaluated for linear and nonlinear models. The model with the lowest Akaike information criterion value was chosen as optimal.

Additional analyses

Metaregression was performed to evaluate the effect of baseline ALT, BMI, and vitamin D, along with changes in vitamin D concentration, on treatment response reflected by changes in ALT and GGT. Treatment effect each outcome was evaluated in different subgroups according to presence of concomitant diabetes, severity of disease (confirmed steatohepatitis), vitamin D compared with calcitriol, treatment schedule (daily, weekly, monthly, and single dose), dose range (therapeutic compared with subtherapeutic, i.e., <2000 IU daily), duration of intervention (shorter or longer than 3 mo), requirement of vitamin D insufficiency for trial enrolment, and the control (placebo compared with usual care). Sensitivity analyses were conducted in exclusion of studies at high or serious risk of bias (ROB).

Quality assessment

ROB 2 and ROB in nonrandomized studies of intervention 2 were used to evaluate each randomized or nonrandomized study's quality, respectively [27,28]. ROB was assessed by 2 independent reviewers for each record and reported for each of the evaluated domains. The overall quality of evidence for select primary outcomes was assessed using the GRADE approach [22,29]. Small-study biases (including publication bias) were examined for ALT and GGT (primary outcomes with a sufficient number of studies) using contour-enhanced funnel plots and Egger's test for plot asymmetry. If suspected, estimates of effect were adjusted for publication bias using a selection model [30].

Results

Study characteristics

A total of 51 possibly relevant records were identified via a search of databases and registers. Information from 33 records pertaining to 28 studies was included in the review (Figure 1). Details regarding the cause of exclusion for possibly relevant records are provided in the supplementary material (Supplemental Table 2). Supplemental Tables 3 and 4 outline the study design characteristics of included studies, along with baseline characteristics of participants in each of these studies. Overall, 21 RCTs (22 intervention arms), 6 single-arm studies (8 intervention arms), and 1 nonrandomized study [12] were reviewed. Half of the included trials (14/28) were single-center studies conducted in various provinces in Iran [13,31–48]. Five studies were conducted in Egypt [12,49–52]. One study was conducted in each of the following countries: Australia, Croatia, Germany, India, Italy, Pakistan, Switzerland, Thailand, and Ukraine [11,

53–60]. The largest study was a single-center trial enrolling 311 patients from a tertiary care center in Croatia. This trial also had the longest intervention duration of 12 mo [54]. Of the 28 studies, 15 had intervention durations of ≤3 mo.

A total of 25 studies used ultrasonography to detect hepatic steatosis. Six of these studies also required a liver FibroScan for diagnostic purposes, and a single study used MRI to confirm evidence of steatosis. Only 3 studies enrolled patients with histologically confirmed steatohepatitis—2 of which were single-arm pilots. Additional inclusion criteria beyond hepatic steatosis—with or without abnormalities in serum aminotransferase concentrations or formal exclusion of nonmetabolic causes for steatosis—were vitamin D insufficiency (17 studies), overweight or obesity (5 studies), diabetes (4 studies), and dyslipidemia or the presence of ≥1 components of metabolic syndrome (1 study each). An additional 4 studies reported baseline vitamin D insufficiency in >80% of the trial participants. The lowest baseline prevalence of vitamin D insufficiency was 48.2% [13]. Five studies did not report the proportion of participants with baseline vitamin D insufficiency.

A total of 20 studies evaluated the effect of a range of daily or weekly oral doses of vitamin D—of which only 1 used ergocalciferol in lieu of cholecalciferol [59]—3 studies used daily calcitriol [33,41,48], 2 used monthly intramuscular injections [12,32], 2 combined an intramuscular loading dose with daily oral doses [49,52], and 1 study reported on a single high-dose intramuscular injection of vitamin D [11]. The daily dose of vitamin D ranged from 1000 to 10,000 IU with weekly doses of 50,000 being the most common (9 of 28 studies).

Qualitative synthesis

Only 1 single-arm pilot evaluated the effect of vitamin D supplementation on histological improvement of steatohepatitis. The study found no significant change from baseline in NAS (5.6 ± 0.9 to 5.5 ± 1.2; *P* value = 0.93) [53]. Similarly, only a single study evaluated the effect of vitamin D supplementation by MRI—finding no significant reduction in hepatic fat fraction [56]. Among noninvasive markers of disease, vitamin D supplementation did not significantly improve FIB-4 or APRI in individual studies [12,48,51]. Similarly, no effect was noted on NFS in either of the 2 studies evaluating the index [12,51]. Findings regarding changes in FLI and CK-18 M30 concentrations were contradictory [56,60,61]. Few adverse events were reported for the intervention. A single case of mild glossitis was reported [56]. Allergy (2 cases), reflux, abdominal cramps, and knee pain (1 case of each) were also reported as adverse events unlikely associated with the intervention [57,58]. No hypercalcemia events were noted in any of the studies.

Meta-analysis

Vitamin D supplementation significantly improved LSM, controlled attenuation parameter (CAP), ALT, AST, GGT, ALP, HOMA-IR, TG, HDL, weight, BMI, and serum 25(OH)D compared with control (Figures 2-4). However, most pooled estimates were accompanied by a high degree of heterogeneity. Only the changes in LSM, ALP, weight, and BMI demonstrated a less than moderate degree of inconsistency (Table 1). Similarly, pooled estimates for change from baseline in LSM, CAP, ALT, AST, GGT, ALP, fasting insulin, HOMA-IR, TG, TC, HDL, weight,

TABLE 1
Mean difference in primary, secondary, and additional outcomes compared with control

Outcome (unit)	Reports included	Pooled sample size	Pooled effect size				Heterogeneity	
			Measure	Effect size	95% CI	*P* value	I^2	τ^2
Primary outcomes								
LSM (kPa)	4	491	MD	−0.52	−0.82, −0.22	0.002	0.0	0.0
CAP (dB/m)	4	491	MD	−24.30	−44.46, −4.13	<0.001	85.5	349.4
ALT (IU/L)	23	1705	MD	−6.64	−9.85, −3.44	<0.001	88.4	44.6
AST (IU/L)	21	1564	MD	−3.18	−5.87, −0.49	0.02	89.9	31.3
GGT (IU/L)	11	897	MD	−5.44	−8.07, −2.81	<0.001	70.7	6.7
ALP (IU/L)	9	563	MD	−10.53	−16.56, −4.50	<0.001	23.0	18.5
Secondary outcome								
HbA1c (mmol/mol)	3	125	MD	−0.17	−0.46, 0.13	0.26	0.0	0.0
FPG (mg/dL)	15	1170	MD	−1.40	−4.50, 1.71	0.38	63.9	15.2
Fasting insulin (μIU/mL)	9	861	MD	−1.35	−3.32, 0.43	0.13	98.4	7.7
HOMA-IR	15	1301	MD	−0.44	−0.78, −0.11	0.01	93.5	0.3
TG (mg/dL)	18	1433	MD	−6.71	−11.24, −2.18	0.004	39.5	22.8
TC (mg/dL)	17	1373	MD	−2.91	−8.84, 3.01	0.34	83.1	100.0
HDL (mg/dL)	18	1391	MD	2.43	0.59, 4.27	0.01	81.2	11.2
LDL (mg/dL)	18	1391	MD	−1.79	−7.76, 4.19	0.56	87.5	120.6
Weight (kg)	12	843	MD	−0.94	−1.80, −0.08	0.03	51.2	0.9
BMI (kg/m^2)	15	1019	MD	−0.37	−0.70, −0.04	0.03	27.5	0.1
WC (cm)	9	694	MD	−0.40	−1.92, 0.11	0.60	77.3	3.4
WHR	3	135	MD	−0.01	−0.02, 0.01	0.48	42.2	0.0
BF%	4	208	MD	−0.30	−0.87, 0.27	0.30	0.0	0.0
Additional outcomes								
25(OH)D (ng/mL)	19	1403	MD	17.29	14.25, 20.33	<0.001	95.9	38.5
Calcium (mg/dL)	4	162	MD	−0.01	−0.10, 0.07	0.78	0.0	0.0

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BF%, body fat percentage; CAP, controlled attenuation parameter; CI, confidence interval; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; LSM, liver stiffness measurement; MD, mean difference; NAS, NAFLD activity score; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio.

TABLE 2
Mean difference in primary, secondary, and additional outcomes compared with baseline

Outcome (unit)	Reports included	Pooled sample size	Pooled effect size				Heterogeneity	
			Measure	Effect size	95% CI	*P* value	I^2	τ^2
Primary outcomes								
LSM (kPa)	6	423	MD	−0.54	−0.71, −0.37	<0.001	0.0	0.0
CAP (dB/m)	6	423	MD	−31.24	−46.47, −16.01	<0.001	93.7	329.1
ALT (IU/L)	31	1224	MD	−9.13	−13.23, −5.03	<0.001	97.8	118.9
AST (IU/L)	29	1143	MD	−3.68	−6.30, −1.05	0.01	96.2	44.3
GGT (IU/L)	12	537	MD	−3.00	−5.47, −0.53	0.02	89.9	10.6
ALP (IU/L)	13	421	MD	−10.00	−17.56, −2.45	0.01	94.0	128.1
T. Bili (mg/dL)	3	80	MD	0.01	−0.09, 0.11	0.78	0.0	0.0
Secondary outcome								
HbA1c (mmol/mol)	5	112	MD	−0.34	−0.79. 0.12	0.14	74.3	0.18
FPG (mg/dL)	20	812	MD	−2.36	−4.83, 0.11	0.06	82.5	18.5
Fasting insulin (μIU/ml)	13	617	MD	−1.36	−2.30, −0.43	0.004	99.9	2.9
HOMA-IR	19	812	MD	−0.46	−0.71, −0.21	<0.001	95.2	0.2
TG (mg/dL)	24	1034	MD	−9.12	−13.51, −4.73	<0.001	72.8	52.8
TC (mg/dL)	24	1016	MD	−6.30	−10.24, −2.36	0.002	84.6	63.8
HDL (mg/dL)	22	946	MD	1.87	0.59, 3.14	0.004	86.5	7.1
LDL (mg/dL)	22	946	MD	−2.02	−5.56, 1.51	0.26	85.1	49.3
Weight (kg)	13	462	MD	−2.38	−3.93, −0.83	0.003	94.1	6.4
BMI (kg/m^2)	17	591	MD	−0.90	−1.37, −0.43	<0.001	86.7	0.6
WC (cm)	9	346	MD	−2.42	−4.80, −0.05	0.046	95.7	11.9
WHR	3	68	MD	−0.01	−0.02, 0.01	0.47	71.4	0.0
BF%	5	136	MD	−1.72	−2.81, −0.64	0.002	79.9	1.1
Additional outcomes								
25(OH)D (ng/mL)	27	1062	MD	17.03	14.77, 19.28	<0.001	97.2	31.2
Calcium (mg/dL)	6	138	MD	0.01	−0.02, 0.03	0.60	0.0	0.0

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BF%, body fat percentage; CAP, controlled attenuation parameter; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; MD, mean difference; NAS, NAFLD activity score; T. Bili, total bilirubin; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio.

BMI, WC, BF%, and serum 25(OH)D showed statistically significant improvements. Only the changes in LSM showed a low degree of heterogeneity (Table 2). No significant alterations in serum calcium were noted when compared with baseline or control. Risk of all-cause study discontinuation was balanced between intervention and control groups (relative risk = 0.94; 95% CI: 0.63, 1.41; $I^2 = 0.0\%$; $\tau^2 = 0.0$).

Pooled and individual estimates for reduction in LSM did not approach the prespecified threshold of 30% reduction in any of the studies. Furthermore, the pooled estimates for reductions in serum ALT compared with control and baseline did not overlap with the prespecified threshold of clinical significance (17 IU/L; Figures 3 and 4). Mean reductions in ALT were >17 IU/L in 3 of 23 and 6 of 31 studies compared with control and baseline, respectively. Among the explored dose-response models, the restricted cubic spline model—with 3 knots placed on the 10th, 50th, and 90th quantiles—had the best performance for both changes in ALT and GGT (Figure 5) compared with control.

Additional analyses

Although some subgroup analyses yielded more consistent results for multiple individual outcomes (Supplemental Sections 1–7), consistency was rarely achieved regarding related outcomes (liver enzyme, glucose regulation, lipid profile, and anthropometric indices). Furthermore, changes in vitamin D (direct response) were not consistent in any particular subgroup.

Only baseline ALT concentrations were found to be an independent predictor of change in ALT from baseline and compared with control in metaregression (both *P* values < 0.001; Supplemental Section 8. The evaluated multivariate regression models had substantial or considerable residual heterogeneity for change in ALT from baseline ($I^2 = 88.14\%$; $\tau^2 = 18.97$) and compared with control ($I^2 = 74.15\%$; $\tau^2 = 16.75$). Addition of changes in vitamin D to the models reduced the residual heterogeneity ($I^2 = 82.99\%$ and $\tau^2 = 21.04$ for change from baseline; $I^2 = 41.46\%$ and $\tau^2 = 6.59$ for comparison to control). None of the evaluated variables was found to be an independent predictor for change in GGT from baseline or compared with control (Supplemental Section 9). Multivariate regression models had moderate residual heterogeneity for change in GGT from baseline ($I^2 = 76.06\%$; $\tau^2 = 11.71$) and low heterogeneity for change in GGT compared with control ($I^2 = 49.31\%$; $\tau^2 = 9.51$). Similar to changes in ALT, the addition of a change in vitamin D as a potential predictor further reduced this residual heterogeneity ($I^2 = 48.27\%$ and $\tau^2 = 8.20$ for change from baseline; $I^2 = 3.62\%$ and $\tau^2 = 0.71$ for comparison to control). The forrest plot for risk of treatment discontinuation (Supplemental Figure 10) and suboptimal dose-response models (Supplemental Figure 11) can be found in the supplementary materials. Effects of age and geographical distribution on vitamin D response were also evaluated in post hoc exploratory analyses (Supplemental Figures 12 and 13).

Quality assessment

Overall, ROB was judged to be low for most of the included studies (Supplemental Table 5). Only 3 trials were identified as being at high or serious ROB, and subsequently, excluded in sensitivity analyses (Supplemental Section 7).

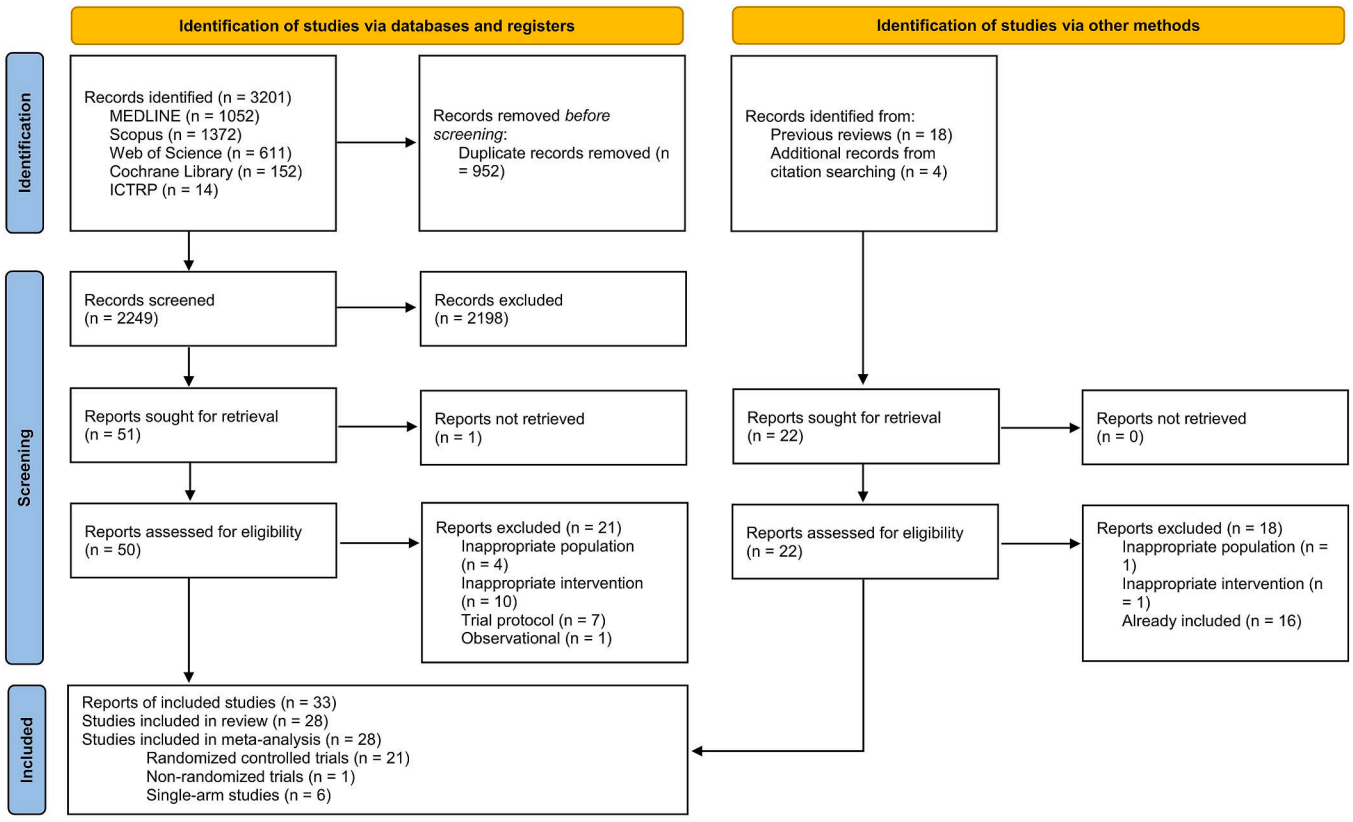

FIGURE 1. PRISMA flow diagram of publications considered in review and meta-analyses. ICTRP, International Clinical Trials Registry Platform.

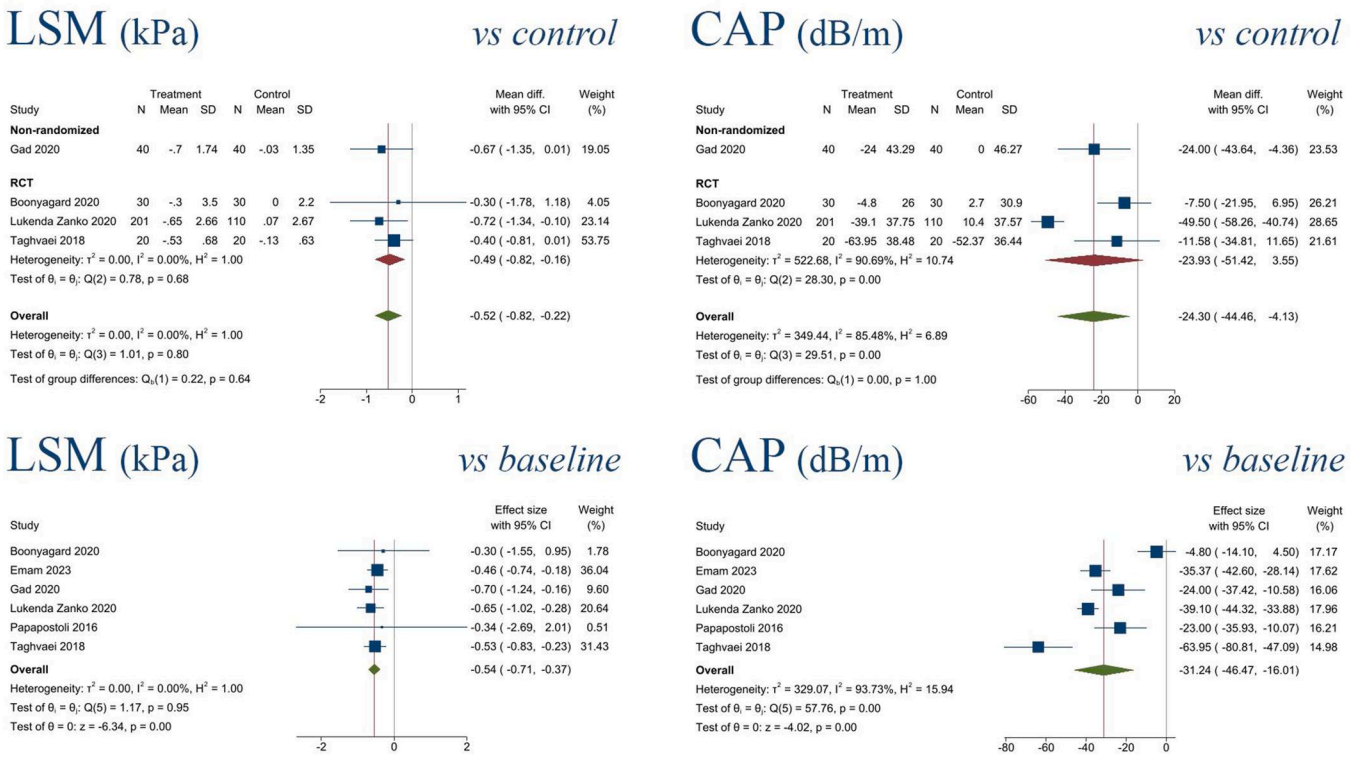

FIGURE 2. Forest plots for meta-analyses of changes in FibroScan LSM and CAP compared with control and baseline. CAP, controlled attenuation parameter; CI, confidence interval; LSM, liver stiffness measurement; RCT randomized controlled trial.

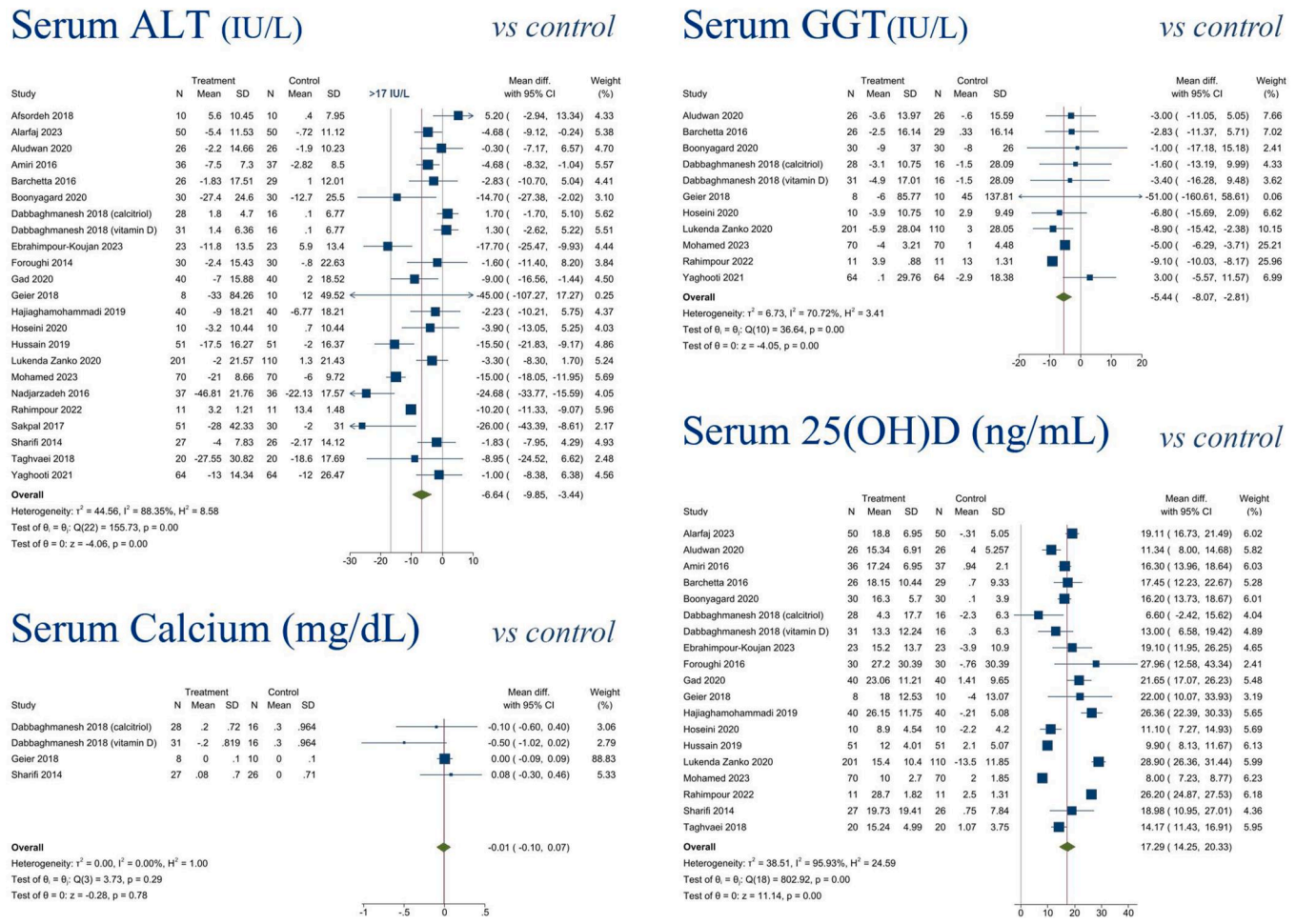

FIGURE 3. Forest plots for meta-analyses of changes in ALT, GGT, vitamin D, and calcium compared with control. Threshold for clinical efficacy regarding changes in ALT was set to a reduction ≥17 IU/L. ALT, alanine aminotransferase; CI, confidence interval; GGT, γ-glutamyl transferase.

Examination of funnel plots for change in ALT from baseline (Egger's test P value = 0.08) and compared with control (Egger's test P value = 0.08) suggested small-study bias. Although some of the plot asymmetry could be attributed to heterogeneity, the weight-function model also yielded more modest adjusted estimates of effect for change from baseline (MD = −4.01; 95% CI: −16.06, 10.99) and compared with control (MD = −2.54; 95% CI: −15.54, 7.52). No small-study bias was identified regarding changes in GGT compared with control (Egger's test P value = 0.32) or from baseline (Egger's test P value = 0.20).

The certainty of evidence regarding most evaluated outcomes was very low to low (Supplemental Tables 6 and 7). Inclusion of evidence from nonrandomized studies did not increase the overall certainty of evidence in any of the evaluated outcomes. Reasons for which the quality of evidence was downgraded included design limitations for estimates of change from baseline; inconsistencies noted regarding all outcomes except for changes in LSM; serious imprecision due to the absence of an obvious clinical benefit regarding most outcomes, and lack of efficacy combined with insufficient information on histological outcomes; and the possibility of publication bias noted for changes in ALT.

Discussion

The current study aimed to systematically review the evidence regarding the safety and efficacy of vitamin D supplementation in adults with steatotic liver disease. Indicators of hepatic outcomes were considered along with multiple metabolic and anthropometric parameters with clinical relevance in the setting of MASLD. Vitamin D supplementation was mostly successful in resolving baseline deficiency and was well-tolerated without any reports of major adverse side effects or hypercalcemia. However, our analysis suggests a lack of meaningful clinical benefit as it relates to improvements in hepatic or metabolic parameters of interest for MASLD. We observed minimal "statistically significant" improvements in FibroScan (LSM and CAP) parameters, liver enzymes (ALT, AST, GGT, and ALP), TG, HDL, and HOMA-IR. Changes in some anthropometric indices from baseline were noted; however, such a finding was not replicated in trials with a comparator. Furthermore, no consistent benefit was noted in the few studies evaluating directly relevant histological outcomes or noninvasive markers of disease (hepatic fat fraction, CK-18, APRI, FIB-4, and NFS).

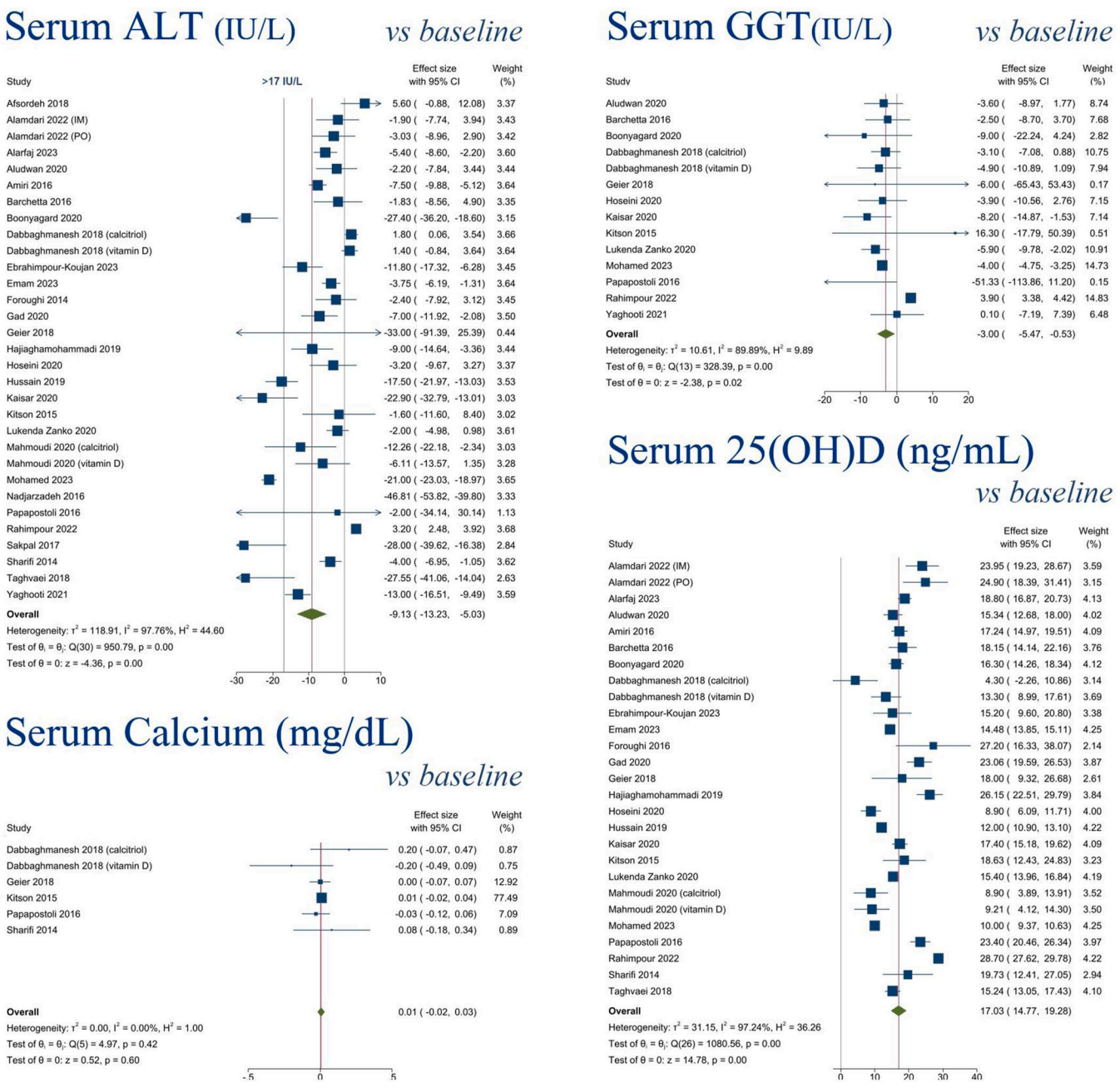

FIGURE 4. Forest plots for meta-analyses of changes in ALT, GGT, vitamin D, and calcium compared with baseline. Threshold for clinical efficacy regarding changes in ALT was set to a reduction ≥17 IU/L. ALT, alanine aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase.

Despite their minimal magnitude, our findings were more consistent regarding changes in liver enzymes when compared with previous reviews [20,21]. However, these benefits, along with those observed in FibroScan parameters, all fell below conventional thresholds for clinical relevance. This effect may be caused by vitamin D-mediated anti-inflammatory and anti-fibrotic effects [62,63]. Vitamin D deficiency promotes hepatic inflammation via activation of the p53–p21 signaling pathway along with toll-like receptors 2 and 4. It also promotes fibrosis via increased hepatic stellate cell proliferation [62]. A negative correlation between vitamin D and ductular reaction has also been noted. In line with the current results, such an effect has been observed to be more pronounced in viral or alcohol-related liver diseases as opposed to MASH [63].

The absence of an appreciable overall benefit regarding metabolic outcomes is also in agreement with recent findings from reviews focusing on individuals with metabolic syndrome [64,65]. However, the findings of a systematic appraisal of the evidence in diabetic patients have suggested a positive effect for vitamin D supplementation in glucose regulation [18]. Similarly, although we found glucose metabolism (with the exception of HOMA-IR) not to be significantly improved in vitamin D-supplemented patients with MASLD, point estimates for the small subgroup with concomitant diabetes trended toward

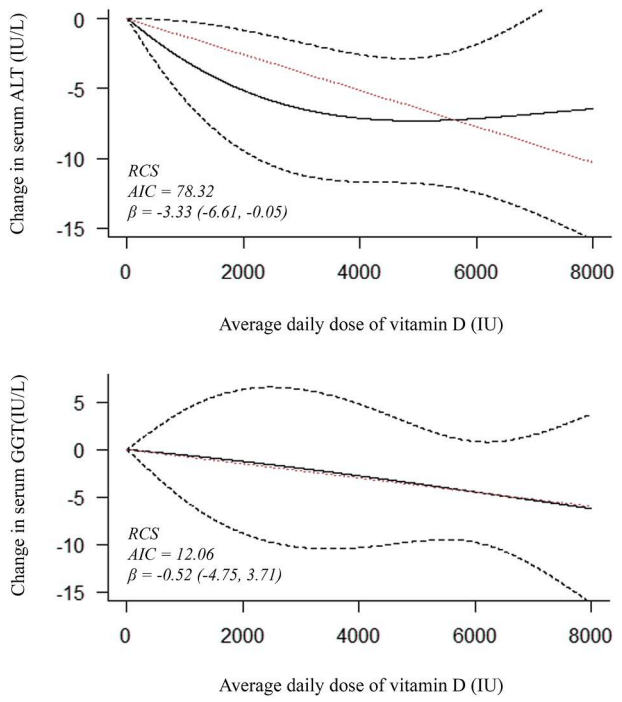

FIGURE 5. Restricted cubic spline (RCS) dose-response model for changes in serum ALT and GGT compared with control. Values for β expressed per 1000 IU of vitamin D. AIC, Akaike information criterion; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase.

improvement. This effect was attributed to improvements in β-cell glucose transport and insulin secretion associated with the vitamin D action. However, both analyses demonstrate further unexplained inconsistencies in the vitamin D effect [18]. The statistical benefit regarding changes in lipid profile (TG and HDL) has also been observed—with a similar small magnitude—in an umbrella-review [66].

Interestingly, both the effects on glucose and lipid metabolism were shown to be more salient in short-term interventions (<3 mo) with higher doses of vitamin D (>2000–4000 IU daily) [18,66]. We also observed such a tendency for these outcomes, as well as most hepatic outcomes. Notable exceptions were changes in FibroScan parameters—found to be more pronounced at longer follow-ups. Although delineating an independent effect for the length of intervention (or effect period) from confirmation of baseline insufficiency is difficult given the overlaps between studies regarding these factors, 6 of 13 interventions longer than 3 mo enrolled participants regardless of baseline vitamin D values, as opposed to only 1 of 18 short-term studies.

Our analysis did not suggest a clear or consistent advantage for any of the vitamin D supplementation regimens evaluated. This is consistent with the findings of a recent large-scale network meta-analysis [67]. Both analyses suggest the efficacy of daily, weekly, or monthly doses of vitamin D supplementation in improving serum 25(OH)D concentrations. The same seems to be the consensus guidance—apart from discouragement of large bolus doses (>100,000 IU) due to possible musculoskeletal adverse events. Use of alternate forms and preparations of vitamin D (other than oral cholecalciferol) also seems not to be warranted sans additional indications e.g. impaired gastrointestinal absorption (for parenteral preparations) or impaired renal tubular function (for use of calcitriol) [61]. Accordingly, our results detected no discrepancy in safety or efficacy between vitamin D preparations or forms. Additionally, despite findings suggesting a doses–response relationship between vitamin D and ALT or GGT changes, we elected not to upgrade the evidence in this regard. This decision followed a paucity of studies without substantial confounding in terms of baseline characteristics, and intervention form or preparation.

Similar to previous meta-analyses on the hepatic or metabolic effects of vitamin D supplementation [18,20,65], a moderate to high degree of inconsistency was noted across our different analyses. The heterogeneity was rarely reduced in subgroup analyses according to trial and population characteristics. Metaregressions by baseline serum 25(OH)D concentrations, ALT, and BMI also failed to account for these inconsistencies. However, the inclusion of vitamin D response as a covariate for changes in ALT and GGT reduced the residual heterogeneity. This suggests the presence of individual or study characteristics affecting vitamin D response, and subsequently the vitamin D-mediated hepatic response—unaccounted for in our analysis. These may include variations by demographic factors (age, sex, or ethnicity) and environmental factors (individual sunlight exposure, latitude, and seasonality). Many of these factors have been underreported or unexplored in the primary literature. Summary vitamin D response was not correlated with mean age in our exploratory analysis (P value = 0.28). Evaluation of response in different age groups was not possible due to a lack of access to individual patient data. Few studies reported sex differences regarding the response, and only 1 study explored sex discrepancies in vitamin D response in MASLD in detail [46]. Such differences in vitamin D metabolism remain understudied even on a larger scale [68]. On the other hand, vitamin D response has been found to vary across different ethnicities—with more pronounced responses in Asian or Caucasian individuals as opposed to those from Middle Eastern or African descent [69]. We were able to somewhat replicate this finding in our exploratory analysis—despite a major limitation due to the uneven geographical distribution of the included trial. Additional underlying genetic and metabolic variations are also of future interest [70].

Considerations

The current review is limited by the parameters of the primary literature. Data were scarce on treatment response in certain patient or intervention subgroups—precluding us from meaningful evaluation of the noted inconsistencies. Several possibly impactful factors were underreported in the primary literature. Additionally, the geographical distribution of the included studies was relatively limited—with most studies being conducted in the Eastern Mediterranean region. The choice of outcome was also suboptimal. Very few studies reported on highly relevant indicators of hepatic outcome, including histological response and reliable noninvasive markers. Furthermore, the evaluated trials failed to analyze and report treatment effects against clinically relevant endpoints. Most of these limitations persisted despite our supplementation of the findings from RCTs with findings from nonrandomized studies.

In conclusion, vitamin D supplementation was generally safe and well-tolerated. However, no meaningful clinical benefit was detected for hepatic or metabolic parameters of interest in

MASLD. The overall quality of the available evidence was very low to low regarding the evaluated outcomes. Furthermore, we were unable to identify any specific subgroup of patients with MASLD reaping further benefits from vitamin D supplementation. We find no justification for recommending evaluation of vitamin D insufficiency or vitamin D supplementation in patients with MASLD beyond standard practice. Future research should explore possible causes of this discrepancy between the promising preclinical results and findings of limited clinical efficacy.

Author contributions

The authors' responsibilities were as follows – ET: contributed to conceptualization, data curation, investigation, writing – original draft; SE: contributed to data curation, investigation, visualization, writing – original draft; FJ, NB, AM-G: contributed to data curation, investigation, writing – review and editing; ZNG: contributed to data curation, writing – review and editing; KS: contributed to formal analysis, investigation, validation, writing – review and editing; MQ: contributed to conceptualization, methodology, project administration, supervision, writing – review and editing.

Conflict of interest

MQ reports financial support was provided by Alborz University of Medial Sciences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

Datasets supporting the conclusions of this manuscript are available on reasonable request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdnut.2025.107631.

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