

Hybrid PHC 2024

Institut Pasteur – Paris March 18 – 19



Translating the Role of Vitamin D Supplementation in Chronic Liver Disease:

SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Vitamin D (VD) deficiency is highly prevalent in chronic liver disease (CLD). Although international societies recommend supplementation in cases of proven deficiency, its impact on CLD remains uncertain. Our aim was to evaluate the effect of VD supplementation in CLD by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods

We systematically searched three databases on 8th November 2022 (PROSPERO: CRD42022370312). Our outcomes involved survival, controlled attenuation parameter (CAP), liver stiffness measurement (LSM), changes in liver enzymes and homeostasis model assessment of insulin resistance (HOMA-IR), among others. Pooled risk ratio (RR), mean difference (MD), and 95% confidence intervals (CI) were calculated using the random-effects model.

Results

Forty-one RCTs were included, comprising 3,562 patients. When comparing the VD group with the control, the overall survival RR was 1.14 (CI: 0.85; 1.54; 4 RCTs) at 6 months and 0.99 (CI:0.83;1.17; 4 RCTs) at 12

	Vitamin D		Control											
Study	Survived	Total	Survived	Total	RR of Survival	RR	95%-CI	Weight						
6 months														
Yokoyama, 2014	42	42	41	42	÷.	1.02	[0.98; 1.07]	17.7%	D1	D2	D3	D4	D5	Overall
Harun, 2020	25	36	23	35		1.06	[0.77; 1.46]	7.2%						
Jha, 2017	35	51	32	50		1.07	[0.81; 1.42]	8.5%						
Mohamed, 2021	103	160	71	168		1.52	[1.23; 1.88]	11.0%	-			+	-	
Random effect	205	289	167	295		1.14	[0.85; 1.54]	44.3%	-	-	(+)	(+)	-	-
$I^2=77\%\;[37\%;92\%]$, τ	= 0.12													
									-	-	•	+	-	-
12 months									-	-	+	X	-	X
Mobarhan, 1984	10	12	6	6		0.84	[0.66; 1.07]	9.8%			$\overline{\mathbf{+}}$	(
Okubo, 2021	15	16	17	17		0.94	[0.83; 1.06]	14.9%						
Vosoghinia, 2016	34	34	33	34	÷	1.03	[0.97; 1.09]	17.4%	+	-	+	+	+	-
Grover, 2022	69	81	62	80		1.10	[0.95; 1.28]	13.7%	+			+	-	
Random effect	128	143	118	137		0.99	[0.83; 1.17]	55.7%						

months. VD resulted in non-significant lower CAP (3 RCTs, MD:-23.50 dB/m; CI:-81.72, 34.72) and LSM (3 RCTs, MD:-0.65 kPa; CI:-1.98;0.68). A significant reduction in HOMA-IR was observed in the VD group (12 RCTs; MD:-0.44; CI:-0.87;-0.01). Alanine aminotransferase (20 RCTs; MD:-3.26 IU/L; CI:-6.37,-0.16) and gamma glutamyl transferase (10 RCTs; MD:-5.15 IU/L; CI:-9.05;-1.25) were significantly reduced.

Conclusion

Our results showed significant differences for ALT, GGT, and HOMA-IR in the VD group. In addition, there were no differences in survival, CAP, and LSM. Further RCTs with adequate power are warranted to clarify the results.



Figure 1. Forest plot showing survival in vitamin D and control groups at 6 and 12 months. CI: confidence interval; RR: risk ratio

	Vitamin D			Control			Vitamin D	HOMA IR change			
Study	Total	Mean	SD	Total	Mean	SD	Form	MD	MD	95%-CI	Weight
longer 3 months											
Abu-Mouch, 2011**	36	-2.20	1.2272	36	0.40	4.9812	D3	←	-2.60	[-4.28; -0.92]	3.2%
Lukenda Zanko, 2020	201	-1.10	6.1113	110	0.50	6.0855	D3		-1.60	[-3.02; -0.18]	4.1%
Lorvand Amiri all, 2017**	37	-0.95	1.2773	72	-0.25	1.1483	Calcitriol		-0.70	[-1.19; -0.21]	11.6%
Sakpal, 2017**	51	-0.10	2.0304	30	0.40	1.6760	not specified		-0.50	[-1.32; 0.32]	8.0%
Sharifi, 2014 ß	27	-0.30	1.9938	26	0.14	1.6900	D3		-0.44	[-1.44; 0.55]	6.6%
Guo, 2022	37	-0.31	0.7200	37	0.07	0.9700	D3		-0.38	[-0.77; 0.01]	12.7%
Barchetta, 2016 ß**	26	0.08	2.4956	29	0.45	2.2124	D3		-0.37	[-1.62; 0.88]	4.9%
Boonyagard , 2020	30	-0.30	2.3000	30	0.00	2.3000	D2		-0.30	[-1.46; 0.86]	5.4%
Yaghooti, 2021**	64	0.00	0.8825	64	-0.10	0.8380	Calcitriol	÷	0.10	[-0.20; 0.40]	13.7%
Random effect	509			434				\diamond	-0.55	[-1.05; -0.05]	70.2%
Prediction interval										[-1.86; 0.76]	
$I^2 = 61\% [19\%; 81\%], \tau = 0.$	51										
shorter 3 months											
Hussain, 2019**	51	-1.30	1.6760	51	-0.07	2.5090	D3		-1.23	[-2.06; -0.40]	7.9%
Hoseini all, 2020**	20	-0.32	0.2722	20	-0.08	0.3172	not specified	=	-0.24	[-0.42; -0.06]	14.7%
Hosseini, 2018	37	-0.40	2.0995	38	-1.22	1.9775	D3		0.82	[-0.10; 1.74]	7.1%
Random effect	108			109					-0.25	[-2.53; 2.04]	29.8%
$I^2 = 81\% [41\%; 94\%], \tau = 0.$	51										
Random effect	617			543					-0.44	[-0.87; -0.01]	100.0%
Prediction interval										[-1.51; 0.63]	
<i>I</i> ² = 65% [34%; 81%], τ = 0.4	44										
Residual heterogeneity: I^2 =	68% [39	%; 83%]. τ	= 0.51					-3 -2 -1 0 1 2 3			
5 ,		. 1,					Decrea	ased with Vitamin D Increased with V	itamin D		

Figure 2. Forest plot showing HOMA-IR change in vitamin D and control groups by length of intervention. CI: confidence interval; MD: mean difference; SD: standard deviation.







Figure 4. Summary Forest plot showing changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) in vitamin D and control groups. CI: confidence interval; MD: mean difference.

Figure 3: (A) Forest plot showing the change in the controlled attenuated parameter (CAP) representing liver steatosis and (B) Forest plot showing the change in the liver stiffness measurement (LSM) representing liver fibrosis. CI: confidence interval; MD: mean difference; SD: standard deviation.

PHC202400004 – Petrana Martinekova