# Hepcidin Levels are Suppressed Despite an Intact Hepcidin Iron Axis in Chronic Viral Hepatitis: A Meta-analysis

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## Introduction

Serum Hepcidin levels in chronic liver We found 1840 studies out of which 33 studies met inclusion criteria. disease (CLD) are proposed biomarkers for Our meta-analysis showed that overall in patients with CLD, serum hepatic iron load, inflammation, hepcidin levels (i) Correlated positively with iron indices, including and fibrosis. Studies correlating serum ferritin (r=0.41, p=< 0.0001), hemoglobin (r=0.21, p= 0.011), serum hepcidin with these factors have yielded transferrin saturation (r=0.15, p=0.01) and negatively with total iron variable results. We carried out a metabinding capacity (r=-0.17, p=0.048). There was no correlation with analysis to understand the effect on serum iron levels (r = 0.07, p =0.333) (ii) Correlated positively with serum hepcidin levels on various aspects serum albumin levels (r=0.19, p =0.007) (iii) Correlated positively of CLD including systemic and hepatic iron with histological iron stores (r = 0.46, p = 0.001) (iv) Correlated levels, inflammation and liver synthetic positively with liver hepcidin mRNA levels (r=0.51, p=0.001) (v) Did capacity. not correlate with grade of inflammation or fibrosis on liver biopsy. On subgroup analysis chronic viral hepatitis differed significantly in that serum hepcidin levels had no correlation with iron indices such as hemoglobin (r=0.14, p=0.534), transferrin saturation (r=0.13, Methods p=0.36) or total iron binding capacity (r=-0.01, p=0.18). There continued to be a positive correlation with ferritin, albumin, hepcidin We searched Pubmed, Embase and Web mRNA and histological iron score.

of Science for studies which measured serum hepcidin levels in patients with CLD from inception till 2020. We included studies where correlation of serum hepcidin levels with serum iron indices, inflammatory markers, grade of inflammation/fibrosis or iron score on liver biopsy was examined. Meta-analysis was done using STATA software applying the random effects model.

## Results

l	Study				Correlation with 95% CI	Weight (%)
	Abbas et al. 2020				0.13 [ -0.12, 0.3	8.33
	Amer et al. 2020				- 0.54 [ 0.25, 0.7	(4) 6.77
	Fujita et al. 2008			2012	-0.23 [ -0.44, 0.0	0] 8.57
	Gao et al. 2018		-		-0.16 [ -0.28, -0.0	3] 10.18
	Girelli et al. 2009			_	0.36 [ 0.15, 0.8	54] 8.77
	Inomata et al. 2019				0.24 [ -0.18, 0.8	5.62
	Lyberopoulou et al. 2015		12. 		0.27 [ 0.05, 0.4	46] 8.77
	Mohamed et al. 2019				0.13 [ -0.15, 0.3	39] 7.72
	Tan et al. 2012			-	0.41 [ 0.32, 0.5	50] 10.41
I	Tsochatzis et al. 2010		_		0.19[-0.01, 0.3	37] 9.08
)	Varghese et al. 2020				0.45 [ 0.23, 0.6	3] 8.26
)	Wang et al. 2016			212 III	0.13[-0.17, 0.4	41] 7.51
	Overall		-		0.21 [ 0.06, 0.3	34]
	Heterogeneity: T <sup>2</sup> = 0.05, l <sup>2</sup> = 81.35%, H <sup>2</sup> = 5.36	6				
	Test of $\theta^{i} = \theta^{i}$ : Q(11) = 75.62, p = 0.00					
	Test of $\theta = 0$ : $z = 2.83$ , $p = 0.00$					۸
		-0.46	0.00	0.46	0.76	A
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Random-ellects REML model

Figure 1 (A)Meta-analysis of serum hepcidin levels showing positive correlation hemoglobin in chronic liver disease

## Discussion

(i) Correlation with hepatic iron levels indicates that hepcidin iron axis is intact in **CLD** including viral hepatitis (ii) Lack of correlation with iron indices indicates that overall hepcidin production is suppressed in viral hepatitis (iii) Serum hepcidin levels likely depend on hepatic synthetic capacity as indicated by a positive correlation with serum albumin.

Girelli et al. 2009 Mohamed et al. 2019 Tsochatzis et al. 2010 Wang et al. 2016 Abbas et al. 2020 Gao et al. 2018 Amer et al. 2020 Inomata et al. 2019 Fujita et al. 2008

### Overall

Heterogeneity:  $T^2 = 0.05$ ,  $I^2 = 76.75\%$ ,  $H^2 = 4.30$ Test of  $\theta^{i} = \theta$ : Q(8) = 37.56, p = 0.00 Test of  $\theta = 0$ : z = 1.59, p = 0.11

Random-effects REML model

## Figure 1(B) Meta-analysis no correlation of serum hepcidin levels with hemoglobin in subgroup with viral hepatitis

Chronic Hepatitis C Girelli et al. 2009 Fujita et al. 2008 Heterogeneity: T<sup>2</sup> = 0.14, |2 = 90.11%, H<sup>2</sup> = 10.11 Test of  $\theta' = \theta'$ : Q(1) = 10.11, p = 0.00

### Non-alcoholic Fatty Liver Disease Marmur et al. 2018

Hoki et al. 2015 Valenti et al. 2011 Heterogeneity: r = 0.00, k = 0.00%, H2 = 1.00 Test of  $\theta' = \theta_i$ : Q(2) = 0.91, p = 0.64

### Alcohol Associated LiverDisease Nahon et al. 2016 Heterogeneity: r2 = 0.00, 12 = .%, H2 = .

Test of  $\theta' = \theta$ : Q(0) = -0.00, p =

## Overall

Heterogeneity: T2 = 0.08, 12 = 84.68%, H2 = 6.53 Test of  $\theta' = \theta'$ : Q(5) = 30.50, p = 0.00 Test of group differences: Qb(2) = 3.03, p = 0.22

Random-effects REML model

Figure 1 (C) Meta-analysis positive correlation of serum hepcidin levels with histological iron scores in all groups





