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ORIGINAL ARTICLE

Role of Endosialin/CD248 and Cytoglobin in Liver Fibrosis

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Abstract

Background: **Chronic liver diseases are a major global health burden. Cytoglobin (Cygb), Human IV globin is abundantly expressed in CSCs between hepatocytes. CYGB can bind oxygen and nitric oxide and is said to protect hepatic stellate cells (HSCs) from reactive oxygen species (ROS).**

Aim: **To estimate role of CD248 and Cygb in the process of liver fibrosis.**

Patients and methods: **This study was conducted on 44 Egyptian patients with hepatic stenosis detected by ultrasound, and 40 healthy volunteers as control group.**

Results: **Our results showed statistically significant (P value < 0.001) increased CD248 in patients group (189.03 ± 66.6) when compared with control group (138.7 ± 36.5), decreased Cygb in the patients group (1.62 ± 0.35) when compared with the control group (1.93 ± 0.26).**

Conclusion: **Our study identified Cygb and CD248 as a novel therapeutic-targets in liver-fibrosis.**

Keywords: CD248, Chronic liver disease, Cygb, Fibrosis

1. Introduction

Chronic liver disease symbolized as a major global health problem with mortality rate 2 million death worldwide each-year.[1]

Risk factors of chronic liver disease were included, hepatitis C-Virus, hepatitis B-Virus, Alcoholic and NonAlcoholic seato-hepatistis, autoimmune and genetic diseases.[2]

Liver fibrosis recognized with the chronic inflammatory disease with mortality rate 45% all-over the world.[3]

Clinically, the treatment of liver cirrhosis emerged with antiviral therapies for viral-hepatitis, change lifestyle, and bariatric surgeries.[4]

Cytoglobin (CYGB) is the human fourth globin antifibrotic target factor which is expressed by hepatocytes.[5]

CD248 is an endo-thelial tumor marker expressed on endo-thelial cells with several types of cancers, such as; the brain and colon. As perprevious studies attempted to apply CD248 markers were expressed in chronic liver injury and highly expressed with liver fibrosis.[6]

Therefore; This study aims to evaluate the role of CD248 and Cygb in the liver fibrosis process and the development of antifibrotic therapies.

2. Patients and methods

In this cross-sectional-study at the Internal Medicine Department, Assiut Faculty of Medicine, Al-Azhar University. 44 Egyptian patients with chronic liver disease were enrolled. 40 patients were divided into two groups; Chronic-liver-disease group: including 44 patients with chronic liver disease. The diagnosis were based on clinical picture, ultrasonography, and laboratory finding. Healthy control group: including 40 age and sex matched healthy volunteers who were normal by clinical, laboratory and radiologic investigations.

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Patients proved as having chronic liver diseases and Age greater than 18 years old were included. Patients who less than 18 years old, end-stage liver disease, other fibrotic diseases and systemic sclerosis, malignancy and Noncompliant patients were excluded.

History and clinical examination: Complete history taking, Full clinical examination include assessment of general condition, vital signs. Abdominal, chest and heart examination were assessed with focus on manifestations of chronic-liver-disease were collected from all patients. Blood pressure equal or more than 140/90 mmHg defined as hypertension. Laboratory Investigations: Complete blood picture (CBC), Liver profile, Renal function tests, Lipid profile and Quantitative detection of Cygb and CD248 in serum.

7 ml of venous-blood was collected from each patient. The collected-sample was allowed to clot for half an hour in a water bath at 37 °C, and then it was centrifuged for 15 min at 3000 revolutions/minute for separation of serum by means of a clean dry Pasteur pipette. 2 ml of blood was put on EDTA (1 mg/ml blood) and mixed thoroughly to perform CBC.

Quantitative detection of CYGB in serum was measured in all patients by enzyme-linked immune-sorbent assay (ELISA) commercial kit (Human Cytoglobin, CYGB ELISA Kit, Chongqing Biospes Co., Ltd, China). This kit was based on standard sandwich enzyme-linked immune-sorbent assay technology. The purified anti-CYGB antibody was precoated onto 96-well plates.

Quantitative detection of CD248 in serum was measured in all patients by enzyme-linked immune-sorbent assay (ELISA) commercial kit. The purified antiEndosialin/CD248 antibody was precoated onto 96-well plates.

Assessment of the liver for its size in both midline and mid-clavicular line, surface of the liver and echogenicity.[7]

The study was approved by Committee of Internal Medicine Department and Committee of Faculty of Medicine and then by the Ethical Committee at Al-Azhar University.

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage.

Table 2. Comparison between studied groups CD248 and Cytoglobin.

	Patients ($N = 44$)	Control ($N = 40$)	MW	P value
CD248 (pg/ml)				
Mean ± SD	189.03 ± 66.6	138.7 ± 36.5	416	<0.001 S
Cygb (ng/ml)				
Mean ± SD	1.62 ± 0.35	1.93 ± 0.26	424	<0.001 S

Table 3. Comparison between studied groups liver function tests.

	Patients ($N = 44$)		Control ($N = 40$)		χ^2	P value
ALT						
Normal	36	81.8%	40	100%	8.03	0.005 S
Elevated	8	18.2%	0	0%		
AST						
Normal	30	68.2%	40	100%	15.3	<0.001 S
Elevated	14	31.8%	0	0%		
Bilirubin						
Normal	32	72.7%	40	100%	12.7	<0.001 S
Elevated	12	27.3%	0	0%		
ALB						
Normal	13	29.5%	10	25%	0.21	0.641 NS
Decreased	31	70.5%	30	75%		
ALP						
Normal	28	63.6%	29	72.5%	0.75	0.385 NS
Elevated	16	36.4%	11	27.5%		

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase.

Table 4. Comparison between studied groups main indices of CBC.

	Patients ($N = 44$)	Control ($N = 40$)	MW	P value
Hb (g/dl)				
Mean ± SD	11.2 ± 2.3	12.8 ± 0.4	478	<0.001 S
WBCs (x10^3/ul)				
Mean ± SD	7.2 ± 3.2	5.9 ± 2.3	666	0.055 NS
PLTs (x10^3/ul)				
Mean ± SD	268.0 ± 150.7	270.5 ± 125.1	853	0.809 NS

PLT, platelets.

3. Results

Highly statistically significant (P value < 0.001) increased CD248 in patients group (189.03 ± 66.6) when compared with control group (138.7 ± 36.5).

Table 1. Comparison between studied groups as regard age and sex.

	Patients ($N = 44$)		Control ($N = 40$)		Stat. test	P value
Age (years)						
Mean ± SD	48.02 ± 15.6		47.8 ± 19.03		$T = 0.054$	0.957 NS
Sex						
Male	11	25%	12	30%	$\chi^2 = 0.26$	0.608 NS
Female	33	75%	28	70%		

Table 5. Comparison between studied groups studied laboratory data.

	Patients ($N = 44$)	Control ($N = 40$)	MW	P value
RBG (mg/dl)				
Mean ± SD	156.7 ± 88.2	100.1 ± 5.1	538	<0.001 S
Total Cholesterol (mg/dl)				
Mean ± SD	174.4 ± 58.4	157.9 ± 11.6	724	0.162 NS
TG (mg/dl)				
Mean ± SD	144.8 ± 73.9	117.4 ± 10.3	792	0.430 NS
Creatinine (mg/dl)				
Mean ± SD	0.86 ± 0.4	0.83 ± 0.2	778	0.356 NS

Table 6. Description of Sonar results in patient's group.

	Patient's group ($N = 44$)	
Sonar results		
Cirrhotic liver	33	75%
Fatty liver	11	25%

Table 7. Relation between Sonar results and liver function tests.

	Sonar results				χ^2	P value
	Cirrhotic ($N = 33$)		Fatty ($N = 11$)			
ALT						
Normal	25	75.8%	11	100%	3.2	0.071 NS
Elevated	8	24.2%	0	0%		
AST						
Normal	20	60.6%	10	90.9%	3.5	0.062 NS
Elevated	13	39.4%	1	9.1%		
Bilirubin						
Normal	22	66.7%	10	90.9%	2.4	0.118 NS
Elevated	11	33.3%	1	9.1%		
ALB						
Normal	9	27.3%	4	36.4%	0.32	0.567 NS
Decreased	24	72.7%	7	63.6%		
ALP						
Normal	17	51.5%	11	100%	8.4	0.004 S
Elevated	16	48.5%	0	0%		

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase.

Table 8. Relation between Sonar results and blood indices of CBC.

	Sonar results		MW	P value
	Cirrhotic ($N = 33$)	Fatty ($N = 11$)		
Hb (g/dl)				
Mean ± SD	11.0 ± 2.5	11.8 ± 1.7	147.5	0.362 NS
WBCs ($x10^3$/ul)				
Mean ± SD	7.1 ± 3.4	7.7 ± 2.9	156.5	0.504 NS
PLTs ($x10^3$/ul)				
Mean ± SD	263.4 ± 163.9	282.1 ± 106.9	157.5	0.521 NS

PLT, platelets.

Highly statistical significant (P value < 0.001) decreased Hb in patients group (11.2 ± 2.3) when compared with control group (12.8 ± 0.4) Tables 1–11.

Table 9. Relation between Sonar results and studied laboratory data.

	Sonar results		MW	P value
	Cirrhotic ($N = 33$)	Fatty ($N = 11$)		
RBG (mg/dl)				
Mean ± SD	137.1 ± 73.4	215.3 ± 105.5	91.5	0.013 S
Cholesterol (mg/dl)				
Mean ± SD	170.2 ± 57.7	187.3 ± 61.2	156	0.504 NS
TG (mg/dl)				
Mean ± SD	140.9 ± 66.5	156.6 ± 95.6	170.5	0.769 NS
Creatinine (mg/dl)				
Mean ± SD	0.88 ± 0.39	0.83 ± 0.31	172	0.810 NS

Table 10. Relation between Sonar results and studied markers.

	Sonar results		MW	P value
	Cirrhotic ($N = 33$)	Fatty ($N = 11$)		
CD248 (pg/ml)				
Mean ± SD	193.1 ± 65.4	176.7 ± 71.9	135	0.216 NS
Cygb (ng/ml)				
Mean ± SD	1.6 ± 0.33	1.68 ± 0.42	173.5	0.831 NS

Table 11. Correlation study between Endosialin, Cygb and other studied data in patient's group.

Variables	CD248		Cygb	
	r	P value	R	P value
age	−0.15	0.332 NS	0.1	0.517 NS
ALT	0.77	<0.001 HS	−0.64	<0.001 HS
AST	0.61	<0.001 HS	−0.52	<0.001 HS
Bilirubin	0.24	0.114 NS	−0.29	0.055 NS
ALB	0.10	0.536 NS	−0.05	0.726 NS
TP	−0.13	0.399 NS	0.32	0.037 S
ALP	0.38	0.011 S	−0.35	0.02 S
Glucose	0.05	0.74 NS	−0.06	0.687 NS
CHOL	0.13	0.409 NS	−0.15	0.319 NS
Tri	−0.05	0.773 NS	−0.04	0.808 NS
Creat	−0.03	0.828 NS	0.02	0.922 NS
Hb	0.23	0.137 NS	−0.23	0.133 NS
WBCs	0.03	0.842 NS	−0.05	0.741 NS
PLTs	−0.13	0.399 NS	0.14	0.369 NS
Endosialin	–	–	−0.83	<0.001 HS
Cygb	−0.83	<0.001 HS	–	–

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; PLT, platelets.

4. Discussion

Chronic liver diseases are a major global health burden and account for ~2 million deaths/year worldwide Wilhelm and colleagues.[8] Therefore; this study was aimed to obtain the role of CD248 and Cygb-markers in liver-fibrosis that targeted the development of antifibrotic-therapies.

Our review results showed no significant-difference between concentrated on group as respect age,

sex, liver capability tests and Cholesterol, fatty substances and serum creatinine. There were 11 (25%) males and 33 (75%) females in patients group while there were 12 (30%) males and 28 (70%) females in control bunch.

In any case, our review observed that measurable critical expanded glucose in patients-group (156.7 ± 88.2) when contrasted and control group (100.1 ± 5.1). As to; realistic discoveries there were 33 (75%) patients with cirrhotic liver and 11 (25%) patients with greasy liver in the concentrated on patients.

In spite of the fact that, our outcomes showed measurable critical (p-esteem <0.001) expanded serum levels of CD248 in patients group (189.03 ± 66.6) when contrasted and control group (138.7 ± 36.5). In concentrate by Wilhelm and colleagues,[8] CD248 articulation was concentrated by immunostaining and quantitative PCR in both ordinary and unhealthy human and murine liver tissue and separated hepatic stellate cells (HSCs). Comparative outcomes were accounted for by Mogler and colleagues,[9] who distinguished the HSC marker CD248 as a basic equilibrium of liver fibrogenesis and regenerative hepatocyte expansion. In accordance with these perceptions, Lin and colleagues[10] analyzed CD248 articulation in the liver tissue of patients with hepatic cirrhosis and in carbon tetrachloride (CCl4)- actuated liver fibrosis in C57BL/6 mice, and affirmed that CD248 was basically communicated in alpha smooth actin (α-SMA)+myofibroblasts. As per the flow study, Smith and colleagues,[11] concentrated on the declaration of the stromal cell marker CD248 in ordinary kidney and in the kidney tissue of a companion of patients with moderate renal illness. IgA nephropathy was picked as a model of moderate human CKD. In harmed fibrotic kidney tissue, CD248 is expanded and communicated on a subpopulation of myofibroblasts notwithstanding a populace of stromal fibroblasts.

Our outcomes showed measurable huge (*P* esteem <0.001) diminished Cygb in patients group (1.62 ± 0.35) when contrasted and control group (1.93 ± 0.26). As per the ongoing review, Motoyama and colleagues,[12] inspected human liver tissues harmed by hepatitis C infection (HCV) disease at different fibrosis stages (from F1 to F4, 10 examples each) and one tissue test harmed by nonalcoholic steatohepatitis (NASH) at fibrosis stage F2 (58-year-elderly person with serum alanine transaminase (ALT) 110 IU/l). They expressed that in human liver tissues harmed by HCV disease at different fibrosis arranges, the quantity of Cygb-positive cells diminishes with fibrosis movement. Comparative outcomes were accounted for by Xu and colleagues,[13] who expressed that overexpression of Cygb safeguarded essential rodent HSCs against oxidative pressure, as evaluated by decreased creation of malondialdehyde and 4-hydroxynonenal, biomarkers of lipid peroxidation. They showed that Cygb, conveyed to liver by rAAV-2 vector, decreases actuation of HSC bringing about less extracellular framework testimony in both poisonous and cholestatic models of liver injury, in any event, when given after the advancement of liver fibrosis.

Results got in this study were in concurrence with Wei and colleagues,[14] who assessed the likely helpful viability of rhCygb in a rodent model of liver sickness prompted by persistent ethanol openness. In Stone and colleagues,[15] Cygb articulation was connected with a more calm aggregate of stellate cells in culture and Cygb was managed by the extracellular framework through integrin motioning in a way subject to enactment of central grip kinase. Additionally, Hui and colleagues,[16] found that cygb showed clear impact contrasted and the benchmark group on Thioacetamide-actuated liver fibrosis in SD rodents, incorporating essentially decline in aspartate aminotransferase, Hyaluronic corrosive, laminin and collagen I (Col I) levels in serum and hydroxyproline in livers, which are the significant files mirroring the level of hepatic fibrosis. In the meantime, the reasonability of rodent hepatic stellate cell line T6 (HSC-T6) cells was restrained by cygb and the apoptosis prompted by cygb in HSC-T6 cells was recognized by Annexin V/PI twofold staining.

In one more review led by Nishi and colleagues,[17] kidney ischemia-reperfusion expanded the quantity of Cygb-positive cells per region and up-managed Cygb mRNA and protein articulation in kidney cortex tissues. Hypoxia up-managed Cygb articulation in refined rodent kidney fibroblasts. The organic capability of Cygb in vivo was assessed in Cygb-overexpressing transgenic rodents. Utilizing both transgenic rodents and refined kidney fibroblasts, it was shown that Cygb articulation presents cell security through a cancer prevention agent component and that heme in Cygb is significant as a result of its antioxidative capacity.

4.1. Conclusion

We found expanding in CD248 in patients-group when contrasted and control-group and diminishing Cygb in patients-group when contrasted and control-group. Cygb and CD248 recognized as a novel therapeutic targeting liver-fibrosis.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

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Conflicts of interest

Conflict of interest statement: The authors declared that there were No conflicts of Interest.

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