TECOmedical Group

Hyaluronic Acid

Biomarker for Diagnosis and Monitoring of Liver Fibrosis and Cirrhosis

- Best biomarker for detection of liver fibrosis - correlates with liver biopsy
- Most specific single marker for assessing the degree of liver fibrosis
- Cost effective and non-invasive to exclude severe fibrosis and cirrhosis
- Accurate monitoring of liver disease in alcoholic patients to exclude cirrhosis
- Early prediction of acute and chronic rejection of liver transplants

HYALURONIC ACID

Serum levels of Hyaluronic Acid (HA) are typically low in healthy individuals as circulating HA is rapidly removed from blood by the liver. A decrease of liver function is immediately reflected by an increase in serum HA levels. This makes HA the perfect marker to diagnose and monitor liver pathologies.

Diagnosis and Monitoring of Liver Fibrosis and Cirrhosis

HA has been extensively studied in patients with different etiologies of liver diseases (Table 1). The serological HA levels correlate with histopathological findings obtained by liver biopsy (Fig. 1) [6, 9] as well with other parameters of liver functions e.g. AST, ALP and GGT [2].

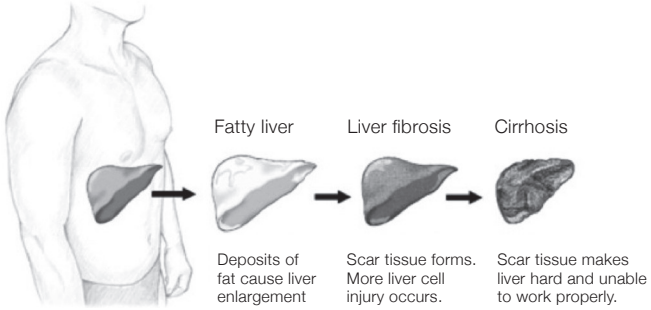


Figure 1: Progression of liver damage leading to liver fibrosis/cirrhosis.

Hyaluronic Acid in Liver Diseases

Etiology	Diagnostig performance of HA	Reference
Hepatitis C Virus (HCV)	100% NPV for cirrhosis	[4]
Hepatitis B (HBV)	90% sensitivity, 98.1% specific for extensive fibrosis	[7]
Alcoholic Liver Disease (ALD)	82,6% sensitivity, 69% specificity for hepatic fibrosis, > Ludwig Stage 2; continous rising HA concentration during progress of liver damage	[9]
Non-alcoholic Fatty Liver Disease (NAFLD)	85% sensitivity, 80% specificity for severe fibrosis	[10]
C282Y Hemochromatosis (HH)	100% sensitivity and specificity for cirrhosis	[1]
Primary Biliary Cirrhosis	Close correlation between serum HA and histopathological changes in the liver. HA is useful to monitor treatment response to ursodeoxycholic acid and budesonide in early stage of PBC.	[13] [14] [16]

Table 1: Diagnostic performance of the biomarker Hyaluronic Acid in patients with different causes of liver disease.

Liver fibrosis and cirrhosis

Serum HA levels increase with the development of liver fibrosis, and correlate with the degree of fibrosis and inflammation (Fig.2).

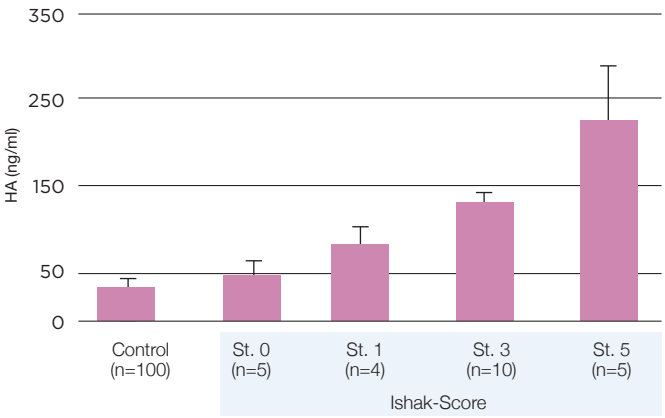


Figure 2: HA concentration in the different fibrotic stages according to ISHAK

Data powered by Bantel, Medizinische Hochschule Hannover

Liver fibrosis and cirrhosis

Serum HA is very helpful to discriminate between insignificant and significant liver fibrosis or to exclude severe fibrosis and cirrhosis as well as to support the monitoring of patients with the risk of progressive fibrosis (Table 2).

Table 2: 405 patients with chronic hepatitis to prospectively predict significant fibrosis, severe fibrosis, and cirrhosis and predict absence of significant fibrosis, severe fibrosis, and cirrhosis [4].

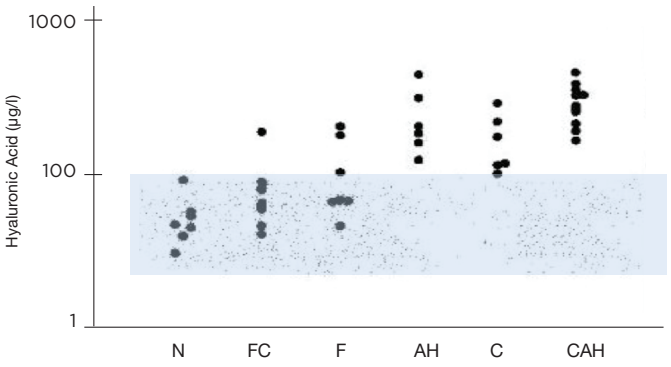
Clinical Interpretation	Sensitivity (%)	Specificity (%)	NPV * (%)	PPV * (%)
Absence of fibrosis	91	36	82	55
Presence of fibrosis	14	99	57	94
Absence of severe fibrosis	78	53	89	34
Presence of severe fibrosis	22	100	81	100
Absence of cirrhosis	100	79	100	20
Presence of cirrhosis	31	99	96	57

*NPV: Negative Predicted Value; PPV: *Positive Predicted Value

Monitoring of Liver diseases in alcoholic patients (ALD)

HA is a particular useful marker to monitor liver disease in alcoholic patients and to exclude cirrhosis with a negative predicted value of 100% [4]. In these patients serum HA reflects the severity of liver inflammation, fibrosis, and fibrogenesis and is a useful marker of precirrhotic and cirrhotic stages (Fig.3).

Figure 3: Serum HA levels in alcoholic patients [8]. Blue area indicates normal values.



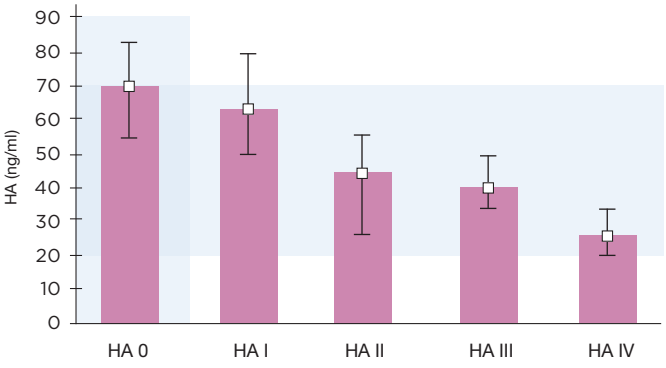
N = normal liver;
FC = fatty changes;
F = fibrosis;
AH = alcoholic hepatitis;
C = cirrhosis;
CAH = cirrhosis with superimposed alcoholic hepatitis

Monitoring of patients with chronic Hepatitis C and B (HCV,HBV)

In patients with chronic hepatitis C virus (HCV), HA levels increase with the development of liver fibrosis. Moreover, in patients with cirrhosis, HA levels correlate with clinical severity [15, 16, 17]. Absence as well as presence of significant fibrosis, severe fibrosis, and cirrhosis can be predicted by HA levels [4].

Serum hyaluronic acid can also help to monitor antiviral or antifibrotic therapies [7]. In chronic viral hepatitis the level of HA decreased in patients responding to antiviral therapy [3, 5]. In patients with chronic hepatitis C serum HA was used to predict the response to interferon therapy where decreasing levels of HA correlated with the histological improvement of liver tissue (Fig.4) [11, 12]. Additionally, the level of serum hyaluronic acid was found to predict the occurrence of severe complications in hepatitis C cirrhosis [13].

Fifure 4: In patients with chronic hepatitis B infection lamivudine treatment decreased the serological concentration of HA [2].



HA 0 = before treatment,
HA I = 4 weeks,
HA II = 12 weeks,
HA III = 24 weeks,
HA IV = 48 weeks of lamivudine treatment (mean ± std.-dev.)

Hyaluronic Acid PLUS – TE1017-2 (CE) / TE1018-2 (RUO)

Sample type	Serum, EDTA-plasma and cell culture supernatant			
Sample preparation	Fasting blood collection.			
Reference values	Hyaluronic Acid Values are dependent on age and gender and influenced by food intake and physical activity. The mean hyaluronic acid concentration was 36.7 ± 23.5 ng/ml. Based on these values a cut-off of 90 ng/ml has been defined.		**Mean ng/ml**	**SD ng/ml**
		Female / Premenopausal	20.1	14.3
		Postmenopausal	50.3	19.9
		Male	42.6	24.6

Table 3: Reference values for female and male persons

Samples from different species, HA forms and HA preparation

Species

	Recovery	
Animal	**Dilution %**	**Spiking %**
Rabbit	110	86
Goat	92	101
Pig	120	87
Dog	109	81
Sheep	99	100
Monkey	104	88
Mouse	86,5	103.5

HA preparations

HA-Form	Mean Recovery
Human HA, blood cord	64%
Chicken Coomb HA	122%
Pharmacopeia Europ. Ref. Std	111%

Note: Samples tested by dilution and spiking recovery

HA forms different Molecular Weight

HA-Form	Mean Recovery
MW 4 – 8 kDa	18%
MW 15 – 40 kDa	29%
MW 90 – 150 kDa	76%
MW > 950 kDa	132%

Literature references

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A EUROBIO SCIENTIFIC COMPANY

Switzerland / Headquarters
TECOmedical AG
Gewerbestrasse 10
4450 Sissach
Phone +41 61 985 81 00
Fax +41 61 985 81 09
Mail info@tecomedical.com

Germany
TECOmedical GmbH
Wasserbreite 57
32257 Bünde
Phone +49 52 23 985 99 99
Fax +49 52 23 985 99 98
Mail info@tecomedical.com

Austria
TECOmedical AG
Phone 0800 20 40 66
Fax 0800 20 40 55
Mail info@tecomedical.com