

# Hyaluronic Acid

## SERUM TEST FOR DETECTING LIVER FUNCTION AND INJURY

### Test Highlights

- Noninvasive liver function assay using serum or plasma.
- Markedly elevated in most patients having liver fibrosis (stage 3 and 4).
- Results less than 55 ng/mL exclude fibrosis in 99 percent of HCV patients.

### Clinical Background

- **Disease Overview**  
Almost all chronic liver diseases result in liver inflammation, which can progress to liver fibrosis and cirrhosis. These diseases include infection (hepatitis B or C), toxicity (alcohol and drugs), genetic (hemochromatosis), autoimmunity, and malignancy.
- **Epidemiology**  
Leading causes of chronic liver disease are viral hepatitis and alcohol abuse. Although only 10-15 percent of patients with alcohol-related liver disease develop cirrhosis, the death rate from this disease in the United States is 12,000 people per year. Chronic viral hepatitis is believed to affect more than four million people in the U.S. Approximately 20 percent of patients with chronic hepatitis C virus (HCV) infection develop fibrosis and cirrhosis. Some will develop hepatocellular carcinoma. People with hereditary hemochromatosis (prevalence of 1 in 400), adverse drug reactions, and autoimmune hepatitis are also at risk for developing liver fibrosis and cirrhosis.
- **Pathophysiology**  
Hyaluronic acid (HA), known also as hyaluronan or hyaluronate, is a glycosaminoglycan polymer that contains ~10 to more than 1,000 disaccharide units, each having a molecular weight of approximately 450 Daltons. HA is widely distributed throughout the body, being produced mainly by fibroblasts and other specialized connective tissue cells, such as hepatic stellate cells. HA has been found to have a structural role in the connective tissue matrix, to participate in cell-to-cell interactions, and exist as a free molecule in synovial fluid and plasma. HA increases rapidly in response to liver injuries. Circulating HA is cleared by the liver (80 percent) and the kidney (20 percent). Thus, liver fibrosis leads to increased HA production and decreased clearance.

### Indications for Use

- Assess the likelihood of liver fibrosis in patients with newly diagnosed chronic HCV infection, potentially reducing the need for liver biopsy.
- Estimate the severity of fibrosis in alcoholic liver disease.
- Substantiate mildly fibrotic liver biopsy results, which lack sensitivity for cirrhosis because of sampling error.
- **Additional Ordering Notes**
  - Fasting specimens are best as HA is slightly increased following a meal.
  - Serum, heparin plasma, and EDTA plasma are acceptable.

### Interpretation

- An ARUP reference interval study using 122 healthy donors established an upper 97.5 percent reference limit of 54 ng/mL.
- No significant differences between adult males and females.
- In chronic HCV patients, HA levels less than 55 ng/mL exclude 99 percent of cirrhosis and 93 percent of fibrosis cases, thus a high negative predictive value.
- Half of patients with high titer HCV RNA results had HA from 55 to 1,000 ng/mL.
- Perhaps the greatest value of HA may be to indicate the absence of extensive fibrosis and cirrhosis, potentially reducing the need for liver biopsy. Almost all patients with significant cirrhosis and fibrosis have elevated serum HA concentrations. Increasing concentrations of serum hyaluronic acid correlates with increasing stage of liver fibrosis. Serum HA has also been proposed as a marker of liver damage from toxic agents, including acetaminophen, ethanol, and bacterial lipopolysaccharide.

Condition	Description	n	Hyaluronic Acid Serum Interval or Mean
Healthy adults	Reference subjects	122	0-54 ng/mL
HCV patients	Fibrosis Stage	486	
	0 (mild)	108	61 ng/mL
	1 (portal expansion)	239	98 ng/mL
	3 (bridging fibrosis)	61	268 ng/mL
	4 (cirrhosis)	78	382 ng/mL
Alcoholic Liver Disease	Fatty liver	22	55 ng/mL
	Fatty liver and fibrosis	20	88 ng/mL
	Fatty liver and inflammation	7	145 ng/mL
	Severe fibrosis and inflammation	26	182 ng/mL
	Cirrhosis	12	1097 ng/mL

### Limitations

- A variety of conditions, including synovial inflammation and cartilage destruction in rheumatoid arthritis, advanced or active osteoarthritis, systemic sclerosis, and systemic lupus erythematosus elevate serum HA.
- HA increases slightly with patient age, ~0.5 ng/mL per year.

### Methodology

- The HA assay is an enzyme-linked binding protein assay that utilizes hyaluronic acid binding protein (HABP) to capture HA. Diluted samples are incubated in HABP-coated microwells to allow the HA present in the sample to bind to the HABP. After washing to remove unbound materials, HABP conjugated to horseradish peroxidase (HRP) is added to form linkages with bound HA. After a second washing to remove unbound conjugate, chromogenic substrate is added and the intensity is measured at 450 nm. The resulting absorbance values are compared to a calibration curve constructed using reference solutions.
- Bilirubin, hemoglobin, lipids, heparin, and EDTA do not interfere with the assay. No cross-reactivity is observed with other glycosaminoglycans.

### Related Tests

Other tests of liver function or injury include (See also Hepatic Function Panel, 0020416): Albumin, Serum or Plasma (0020030); Alkaline Phosphatase, Serum or Plasma (0020005); Aspartate Aminotransferase, Serum or Plasma (0020007); Alanine Aminotransferase, Serum or Plasma (0020008); Protein, Total, Plasma or Serum (0020029); Bilirubin, Total, Serum or Plasma (0020032); Gamma Glutamyl Transferase (0020009); Alpha-2-Macroglobulin (0050005); and Prothrombin Time (0030215).

### References

1. Afdhal NH and Nunes D. Evaluation of liver fibrosis: a concise review. *Am J Gastroenterol* 2004; 99:1160-74.
2. McHutchison JG, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. *J Gastroenterol Hepatol* 2000; 15:945-51.
3. Stickel F, et al. Serum hyaluronate correlates with histological progression in alcoholic liver disease. *Eur J Gastroenterol Hepatol* 2003; 15:945-50.

## Test Information

**0081138**

**Hyaluronic Acid, Serum**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).