Research Article

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Role of measurement of hyaluronic acid in NAFLD

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Role of serum hyaluronic acid in predicting necroinflammatory activity of the nonalcoholic fatty liver disease

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Abstract

Background and Aim: Hyaluronic acid (HA), a fundamental component of the extracellular matrix, is associated with chronic liver diseases. The aim of this study was to investigate quantitative HA measurement as a noninvasive marker for steatosis and fibrosis staging in nonalcoholic fatty liver disease (NAFLD) with biopsy evidence.

Materials and Methods: In this study, 52 NAFLD patients with biopsy evidence and who met the inclusion criteria were included. Hepatic enzyme levels, HA levels, and other laboratory findings were examined. In addition, the degree of steatosis was determined via computed tomography (CT).

Results: According to the degree of steatosis, HA levels were 29.17±22.66, 39.85±60.28, and 32.05±19.40, respectively, and no significant difference was found between the groups (p=0.584). In addition, HA levels were not found to be significant according to the degrees of steatohepatitis (p=0.860). However, a statistically significant relationship was found between steatosis levels detected by CT and biopsy (p<0.01).

Conclusion: Serum HA level, other biochemical parameters, and steatosis severity measurement via CT did not appear to have any diagnostic value for nonalcoholic steatohepatitis. In this context, novel markers that may be useful for NAFLD diagnosis and severity assessment in risky individuals should be investigated.

Keywords: Computed tomography; hyaluronic acid; nonalcoholic fatty liver disease.

Introduction

Globally, nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease,[1] and it is defined by the presence of 5% hepatic steatosis (HS) in the absence of other liver disease etiologies. Nonalcoholic steatohepatitis (NASH) is characterized by the presence of 5% HS and inflammation together with hepatocyte damage, with or without fibrosis.[2-4] NASH may progress to end-stage liver disease and complications, including hepatocellular carcinoma.[5,6]

NAFLD is one of the most common causes of liver enzyme elevation in adults.[7] Most patients with NAFLD have normal serum aminotransferase levels [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] at the time of diagnosis. Although higher AST is associated with the presence of NASH, more than half of people with NASH have normal liver enzyme levels. Consistent with this finding, ALT and AST levels are normal in 44% and 65% of patients with fibrosis, respectively.[5] However, liver enzyme tests can be significantly affected by differences between laboratories.[8] In addition, many noninvasive tests are currently attempting to clinically evaluate NAFLD, especially in fibrosis staging.[1,9]

Hyaluronic acid (HA), a fundamental component of the extracellular matrix in almost every tissue of the body, is mostly synthesized by hepatic star cells and broken down by sinusoidal endothelial cells, and HA level is thought to be correlated with the histological stages of the liver fibrosis.[10] The role of HA in inflammation leading to liver damage has been demonstrated in related studies.[11,12] HA may perform similarly or better in detecting cirrhosis compared with other serum markers such as type III procollagen, type IV collagen, YKL-40, and tissue inhibitor of metalloproteinases. HA concentration is low in healthy liver, whereas HA levels are elevated in the fibrotic liver.[10,13,14]

Liver biopsy remains the gold standard for staging and detecting HS and fibrosis.[6] However, liver biopsy is impractical as it is invasive and costly.[15] Owing to the risk of complications and cost ineffectiveness, liver biopsy is almost never repeated.[16] Histological lesions of NASH may not dissipate homogeneously in the liver parenchyma, which can lead to biopsy sampling errors.[9,17] A number of noninvasive imaging examinations are widely used for the diagnosis of NAFLD, such as abdominal ultrasound, fibroscan, computed tomography (CT), and magnetic resonance elastography, each with different advantages and disadvantages.[18] Measuring the absolute or relative amounts of visceral and subcutaneous fat in the abdomen using CT images can help identify individuals with possible NAFLD.[19] In line with this information, the aim of this study was to investigate HA as a noninvasive marker for measuring steatosis and fibrosis staging in NAFLD patients with biopsy evidence, by comparing it with liver enzymes (ALT, AST) and CT.

Materials and Methods

Study Sample

A preliminary interview was performed with patients who applied to the gastroenterohepatology outpatient clinic between August 2003

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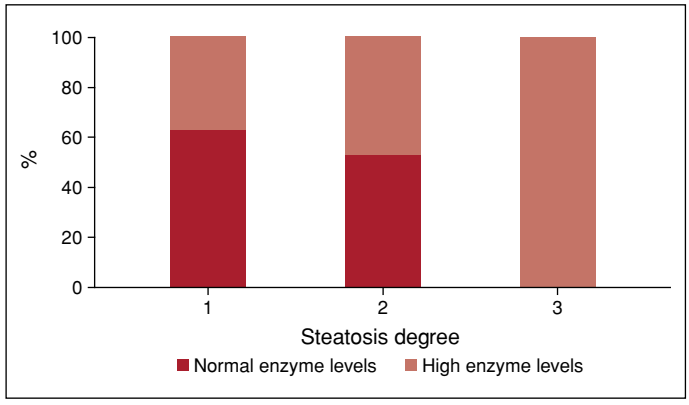

Figure 1. Steatosis distribution of groups by biopsy.
Biopsies of the patients were performed between August 2003 and February 2004.

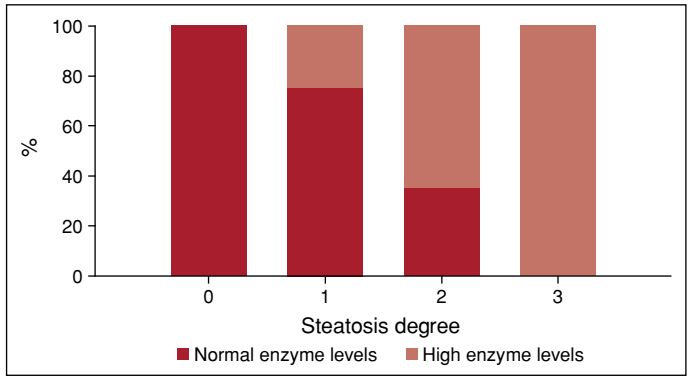

Figure 2. Steatosis distributions of groups by computed tomography.
Computed tomographies of the patients were performed between August 2003 and February 2004.

and February 2004 and who were diagnosed with hepatosteatosis after whole abdominal USG. A total of 52 patients who agreed to undergo liver biopsy were included in this study. Of these 52 patients, 26 had normal aminotransferase levels and 26 had aminotransferase levels 1.5 times above normal. Written consent was obtained from all patients. Patients with steatohepatitis were grouped according to disease severity (0-1 and 2-3) and liver enzyme levels (normal and elevated), and the groups were compared in terms of accepted risk factors for NAFLD, HA levels, and CT results.

The exclusion criteria included the following:

1. Presence of viral liver diseases.
2. Presence of autoimmune liver diseases and positive antinuclear antibody, antismooth muscle antibody, antimitochondrial antibody, and antiliver/kidney microsomal antibody test results.
3. Presence of alcohol-related liver disease, i.e., >40 g of alcohol per week.
4. Presence of metabolic liver diseases, such as alpha-1 antitrypsin deficiency, hemochromatosis, and Wilson's disease.
5. Diagnosis of toxic liver disease (environmental and occupational) in the last 6 months.
6. Having used drugs known to cause NAFLD in the last 6 months.
7. Having used any of the drugs used in the treatment of NASH in the last 6 months.
8. Having undergone gastrointestinal surgery.
9. Presence of biliary obstruction and primary biliary cirrhosis.
10. Pregnancy.
11. Those who have lost 20% of their body weight in the last 3 months.
12. Cancer patients.
13. Patients with comprehension and adjustment disorders.
14. Patients over 65 years of age.
15. Patients receiving total parenteral nutrition treatment in the last 6 months.

Laboratory Findings

AST, ALT, ALT/AST ratio, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase, glucose, total bilirubin (TB), direct bilirubin (DB), total protein, albumin, globulin, albumin/globulin ratio, cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, iron, total-iron binding capacity, ferritin, C-reactive protein, hemoglobin A1c (HbA1c), and HA levels were measured biochemically.

Liver Biopsy and CT

After physical examinations and blood tests, all patients were given appointments for liver biopsy and CT. Liver biopsies were performed in the gastroenterology ward by the same specialist from the radiology clinic. Liver biopsies were taken to the pathology laboratory inside formol-containing solutions and samples were evaluated according to Brunt classification with hematoxylin-eosin, PAS, PAS-D, and reticuline dyes. Before the biopsy, intravenous access was established, peripheral venous blood was taken from the patients, and stored in the freezer below −20°C for HA measurement. HA levels were then measured quantitatively as nanograms/milliliters (ng/ml) from the stored blood using an HA test kit (Corgenix, Broomfield, CO, USA). An average of five liver sections were taken for CT examination, and the severity of steatosis was rated between 0 and 3 by the same specialist in the radiology clinic.

Steatosis and Fibrosis Assessment

Steatosis severity was assessed using the following criteria:

Grade 0: Normal.

Grade 1: Liver attenuation is slightly less than that of the spleen.

Grade 2: The difference between liver and spleen attenuation is more pronounced, and intrahepatic vessels are not visible or their attenuation is slightly greater than the liver.

Grade 3: Significant reduction in liver attenuation with significant contrast between liver and intrahepatic vessels.

NASH was diagnosed in the presence of steatosis and two of the following three features in the center of the third region:

1. Presence of necroinflammatory focus together with mononuclear cells (MNH) and/or neutrophils.
2. Ballooning lesion in hepatocytes with or without Malory object.
3. Presence of pericellular fibrosis.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences) program for Windows 10.0 was used for statistical analysis. Descriptive statistics were present-

Table 1. Characteristics of the participants according to the presence of NAFLD with normal and elevated transaminases

	Normal enzyme level (n=26)	High enzyme level (n=26)	p
Age (years)	44.69±6.02	46.38±8.31	0.405
Cholesterol (mg/dL)	217.65±41.70	224.85±51.26	0.581
Triglyceride (mg/dL)	185.11±105.33	181.92±98.54	0.911
AST/ALT	0.87±0.21	0.68±0.14	0.001
ALP (IU/L)	205.04±57.10	220.73±91.76	0.463
GGT (U/L)	40.73±29.15	58.23±33.70	0.050
Total bilirubin (mg/dL)	0.49±0.21	0.77±0.39	0.002
Direct bilirubin (mg/dL)	0.11±0.04	0.16±0.10	0.033
Albumin/globulin	1.36±0.15	1.38±0.15	0.765
Iron (µg/dL)	77.19±29.67	103.00±39.27	0.010
Ferritin (mL/ng)	58.47±77.98	133.77±114.92	0.001
C-reactive protein (mg/L)	7.08±5.96	8.20±10.33	0.978
HbA1c (%)	6.01±1.14	5.97±1.10	0.894
HA level	24.91±12.59	41.30±52.10	0.272
Gender			0.099
Male	1 (4)	6 (23)	
Female	25 (96)	20 (77)	
Diabetes			0.588
Normal	13 (50)	14 (54)	
Prediabetes	5 (19)	7 (27)	
Diabetes	8 (31)	55 (19)	
Steatosis degree			0.007
1	17 (65)	10 (38)	
2	9 (35)	8 (31)	
3	0 (0)	8 (31)	
Steatohepatitis degree			0.390
0	1 (4)	1 (4)	
1	21 (81)	16 (61)	
2	4 (15)	8 (31)	
3	0 (0)	1 (4)	
Fibrosis stage			0.308
0	23 (89)	20 (77)	
1	3 (11)	4 (15)	
2	0 (0)	2 (8)	
CT stage			0.002
0	7 (32)	0 (0)	
1	9 (41)	3 (17)	
2	6 (27)	11 (61)	
3	0 (0)	4 (22)	
Cholesterol level			0.687
Normal	14 (54)	11 (42)	
25% less than normal	10 (39)	13 (50)	
25% more than normal	2 (7)	2 (8)	
Triglyceride level			0.849
Normal	15 (58)	17 (65)	
25% less than normal	6 (23)	5 (19)	
25% more than normal	5 (19)	4 (15)	

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; HA: Hyaluronic acid; CT: Computed tomography; HbA1c: Hemoglobin A1c. Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as numbers and percentages.

ed as mean and standard deviation. Student's t-test or the Mann-Whitney U test was used to compare quantitative data between the groups. The Chi-squared test and Fisher's exact Chi-squared test were used to compare intergroup qualitative data. Results were evaluated within a 95% confidence interval. Statistical significance was indicated by $p<0.05$.

Results

Table 1 shows the characteristics of patients diagnosed with NAFLD. Of these 52 patients, 26 had normal aminotransferase levels and 26 had aminotransferase levels 1.5 times above normal. ALT/AST ratio, GGT level, TB, DB, iron, and ferritin levels were higher in patients with high enzyme levels than in those with normal enzyme levels ($p<0.05$). AST/ALT ratio was significantly higher in patients with normal enzyme levels than in those with high enzyme levels ($p<0.05$). There was no significant difference between patients with normal and high enzyme levels in terms of sex, diabetes, and histopathological distribution of steatohepatitis and fibrosis stages ($p>0.05$).

The ratio of patients with a steatosis degree of 1 in liver biopsy was significantly higher in patients with normal enzyme levels than in patients with high enzyme levels ($p<0.01$) (Fig. 1).

A significant intergroup difference was found in terms of the CT results ($p<0.01$). The ratio of patients with a CT result of 1 and normal enzyme levels was significantly higher than those with high enzyme levels, whereas the ratio of patients with a CT result of 2 and high enzyme levels was significantly higher than those with normal enzyme levels ($p<0.05$) (Fig. 2).

In patients with high enzyme levels, there was a significant relationship between steatohepatitis and diabetes ($p<0.05$). The incidence of no diabetes and chemical diabetes in patients with a steatohepatitis rating of 0-1 was significantly higher than in patients with a steatohepatitis rating of 2-3. However, the incidence of diabetes was significantly higher in patients with a steatohepatitis rating of 2-3 than in patients with a steatohepatitis rating of 0-1 (Table 2).

In patients with normal enzyme levels, no statistically significant difference was found between the CT results of patients with a steatohepatitis degree of 0-1 and those with a steatohepatitis degree of 2-3 ($p>0.05$). In patients with high enzyme levels, no statistically significant difference was found between the CT results of patients with a steatohepatitis degree of 0-1 and those with a steatohepatitis degree of 2-3 ($p>0.05$) (Table 3).

No significant difference was found between steatosis levels in terms of HA ($p>0.05$). However, a statistically significant relationship was found between steatosis levels detected by CT and biopsy ($p<0.01$) (Table 4). No significant difference was found between steatohepatitis levels with respect to HA ($p>0.05$). No significant relationship was found between steatohepatitis levels and the CT method ($p>0.05$) (Table 5).

Table 2. Comparison of risk factors with respect to steatohepatitis

	Steatohepatitis degree		p
	0-1	2-3	
Normal enzyme levels			
ALT	26.23±8.51	34.25±4.03	0.064
ALT/AST	1.21±0.28	1.15±0.11	0.499
AST/ALT	0.87±0.22	0.87±0.09	0.594
Ferritin	46.33±27.21	125.25±196.14	0.619
Albumin/globulin	1.35±0.15	1.42±0.17	0.569
C-reactive protein	7.14±6.44	6.72±2.38	0.720
HA level	25.37±13.64	22.36±2.70	0.972
	n (%)	n (%)	
High age			1.000
≤45	14 (64)	3 (75)	
>45	8 (36)	1 (25)	
Body mass index			1.000
Normal	4 (18)	0 (0)	
Obesity	18 (82)	4 (100)	
Diabetes			0.227
Normal	12 (55)	1 (25)	
Prediabetes	3 (14)	2 (50)	
Diabetes	7 (32)	1 (25)	
High enzyme levels			
ALT	63.35±18.69	57.56±11.64	0.626
ALT/AST	1.57±0.31	1.43±0.28	0.571
AST/ALT	0.66±0.13	0.72±0.15	0.535
Ferritin	130.62±126.48	139.72±96.00	0.726
Albumin/globulin	1.39±0.16	1.35±0.13	0.666
C-reactive protein	6.38±4.40	11.65±16.56	0.289
HA level	46.08±63.11	32.28±19.39	0.872
	n (%)	n (%)	
High age			1.000
≤45	8 (47)	4 (45)	
>45	9 (53)	5 (55)	
Body mass index			1.000
Normal	4 (24)	2 (22)	
Obesity	13 (76)	7 (78)	
Diabetes			0.048
Normal	10 (59)	4 (44)	
Prediabetes	6 (35)	1 (12)	
Diabetes	1 (6)	4 (44)	

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma -glutamyl transferase; HA: Hyaluronic acid; CT: Computed tomography; HbA1c: Hemoglobin A1c. Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as numbers and percentages.

Discussion

NAFLD covers a wide spectrum of liver damage. It can be combined with a large number of different etiologies, and the natural course of the disease varies according to the underlying cause. The clinical picture may be innocent or may carry a significant risk of liver-related morbidity and mortality owing to severe necroinflammation and fibrosis.[20,21] Therefore, it is extremely important to identify risk groups in patients diagnosed with NAFLD, to identify patients at risk of NASH and cirrhosis during follow-up, and to have reliable diagnostic methods. Although changes in nutrition and life habits and weight control are extremely important in treatment, there is still no successful pharmacotherapy. Therefore, repeatable noninvasive tests in treatment follow-up are becoming more important for patients and clinicians. In this context, quantitative HA value was examined in the present study as a noninvasive marker in a total of 52 patients diagnosed with hepatosteatosis by USG.

Table 3. Comparison of CT findings with respect to steatohepatitis degree

	Steatohepatitis		p
	0-1	2-3	
Normal enzyme levels			
CT rating			0.228
0	7 (39)	0 (0)	
1	6 (33)	3 (75)	
2	5 (28)	1 (25)	
High enzyme levels			
CT rating			0.555
1	3 (23)	0 (0)	
2	7 (54)	4 (80)	
3	3 (23)	1 (20)	

Categorical variables are expressed as numbers and percentages.

Table 4. Relationship between steatosis and hyaluronic acid

	Steatosis degree detected by biopsy			p
	1	2	3	
Hyaluronic acid	29.17±22.66	39.85±60.28	32.05±19.40	0.584
CT rating				0.001
0	6 (27)	1 (8)	0 (0)	
1	8 (36)	4 (34)	0 (0)	
2	8 (36)	7 (58)	2 (33)	
3	0 (0)	0 (0)	4 (67)	

Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as numbers and percentages.

Table 5. Relationship between steatohepatitis, hyaluronic acid, and CT

	Steatohepatitis		p
	1	2	
Hyaluronic acid	35.39±44.39	29.23±16.59	0.860
CT rating			0.434
0	7 (23)	0 (0)	
1	9 (30)	3 (33)	
2	11 (37)	5 (55)	
3	3 (10)	1 (12)	

Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as numbers and percentages.

In the present study, the ratio of patients with steatosis degree of 1 detected by the CT method was significantly higher among patients with normal enzyme levels than among patients with high enzyme levels, whereas the ratio of patients with steatosis degree of 2 was significantly higher in patients with high enzyme levels than in patients with normal enzyme levels ($p<0.01$). No statistically significant difference was found between the CT results of patients with a steatohepatitis degree of 0-1 and 2-3 ($p>0.05$). In parallel with this finding, literature evidence shows that CT is not as useful as biopsy in determining the degree of steatohepatitis.[22,23] However, owing to the limitations and risks of liver biopsy, the role of noninvasive tests is important, and they are being more commonly used to classify the stage of liver disease, predict outcomes, and/or monitor the treatment response.[24]

In the present study, there was no significant difference between the two groups classified according to enzyme levels in terms of HA levels ($p>0.05$). In addition, there was no significant difference between HA levels of patients with a steatohepatitis degree of 0-1 and patients with a steatohepatitis degree of 2-3 ($p>0.05$). As the number of patients with F2 fibrosis grade (n=2) was low in our study, it is thought that there may not be a significant relationship between HA levels. As HA is valuable for fibrogenesis, prospective controlled biopsy studies should be conducted especially with risk groups for fibrosis in NAFLD. HA may be useful in NAFLD not for screening but as a test for assessing and monitoring risky cases. Serum HA levels can be used to predict patients with cirrhosis and monitor the response to treatment. High HA blood levels have been reported in different liver diseases. HA density is approximately 15 times higher than normal in the cirrhotic liver.[25] In chronic hepatitis C patients, HA levels were found to be effective in distinguishing fibrosis scores.[26] A significant decrease in serum HA concentration was reported in patients responding to antiviral therapy at the end of follow-up compared with initial values.[27] In a study covering 41 centers, 486 HCV-diagnosed patients underwent biopsies, which revealed the presence of a correlation between serum HA levels and fibrosis. In addition, HA levels increased as the degree of fibrosis increased.[14] HA levels were higher in HBeAg-positive patients compared with HBeAg-negative patients.[28] A significant increase was found in HA levels in chronic hepatitis B in parallel with fibrosis levels from mild fibrosis to advanced fibrosis. It was reported that HA levels may be an indicator of the presence of fibrosis in NAFLD, HIV and HCV coinfection, alcoholic liver disease, primary biliary cirrhosis, biliary atresia, and hereditary hemochromatosis patients.[10]

Our study has some limitations. One of these is the diagnosis of hepatosteatosis of the patients included in our study by USG instead of CT. In addition, the low number of patients with advanced fibrosis in the study is another limitation. In the present study, serum HA level, other biochemical parameters, and assessment of steatosis severity by CT were not found to have any diagnostic value in NASH cases. Large-scale prospective studies comparing results with biopsy are needed before clinical, biochemical, and imaging techniques can be used to predict the degree and stage of the disease without a liver biopsy. Clinicians can offer individualized plans to patients based on risk assessment. At-risk individuals can be identified and referred to relevant clinics early on for further tests that can confirm and determine NAFLD severity. Therefore, with early lifestyle changes and medical interventions, the disease can be controlled and significant risks can be eliminated.

Ethics Committee Approval: This study was conducted retrospectively.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HG, OOK; Design – HG, OOK; Supervision – HG, OOK; Data Collection and/or Processing – HG; Analysis and/or Interpretation – HG; Literature Search – HG; Writing – HG; Critical Reviews – OOK.

Conflict of Interest: The authors have no conflict of interest to declare.

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