Low plasma apolipoprotein A-I level: new prognostic criterion in childhood cirrhosis?

Mukadder Ayşe Selimoğlu, Sema Aydoğdu, Raşit Vural Yağcı

Gastroenterology and Nutrition Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey

SUMMARY: Selimoğlu MA, Aydoğdu S, Yağcı RV. Low plasma apolipoprotein A-I level: new prognostic criterion in childhood cirrhosis? Turk J Pediatr 2001; 43: 307-311.

Apolipoprotein A-I (apo A-I) has been found to be decreased in adults with cirrhosis, but it has not been routinely used for prognostic purposes thus far. This study was performed to determine apo A-I levels in childhood cirrhosis and to establish some prognostic cut-off values. Apo A-I levels of 78 children with chronic liver disease, 38 of whom had cirrhosis as well, were studied. Mean values of cirrhotic, non-cirrhotic and healthy children were not different ($p > .05$). However, in cirrhotic children, the highest value was detected in the Child-Pugh A group, and it was different from those of the B and C groups ($p < .05$ and $p < .001$, respectively). Apo A-I was the lowest in the moderate risk group of Malatack's model, and was significantly different from the low risk group ($p < .05$). Apo A-I was inversely correlated with Malatack score, Child-Pugh score, total bilirubin, conjugated bilirubin, and prothrombin time ($p < .01$, $p < .01$, $p < .01$, $p < .01$, $p < .05$, respectively). In cirrhotic children with cholestasis, apo A-I was lower than in non-cholestatic children ($p < .05$). Apo A-I value < 80 mg/dl had 84% specificity and 84% negative predictive value for the high risk group of Malatack's model. Similarly, Apo A-I value < 83 mg/dl had 95% specificity and 87% negative predictive value for the Child-Pugh C group.

We concluded that Apo A-I is a sensitive and specific parameter of poor prognosis in childhood cirrhosis.

Key words: apolipoprotein A-I, cirrhosis, prognosis, children.

Apolipoprotein A-I (apo A-I) is the major protein of high-density lipoprotein cholesterol (HDL) and is primarily synthesized in the liver and small intestine. It is secreted as pro apo A-I, and by pro apo A-I converting enzyme, it becomes mature[1]. Plasma apo A-I level is a routine test evaluating lipid profile in diseases affecting lipid metabolism. It has been found that serum pro apo A-I converting enzyme activity is decreased in patients with acute liver disease and cirrhosis, diseases in which alterations of lipid metabolism is observed[1-5]. However, to the best of our knowledge, clinicians have not used this parameter as a prognostic criterion in childhood cirrhosis thus far. In this study, we investigated plasma apo A-I levels in respect to the other well known prognostic criteria in children with cirrhosis.

Material and Methods

Thirty-eight children with cirrhosis and 40 children with chronic liver disease without cirrhosis, followed by Ege University Pediatric Gastroenterology and Nutrition Department, and 20 healthy children were included in this study. Mean age of the patients was 10.0 ± 4.9 years (3 months-20 years) and of the healthy children was 8.8 ± 5.8 years. Diagnosis of cirrhosis and chronic liver disease as based on physical examination, laboratory investigations, and liver biopsies. Of cirrhotic patients, 11 had Wilson's cirrhosis, seven had autoimmune hepatitis, four had biliary atresia, four had paucity of intrahepatic bile ducts and 12 had cryptogenic cirrhosis. Of patients with chronic liver disease, 36 had chronic hepatitis B infection and four had metabolic disease (not lipid metabolism disorder). For the determination of the prognosis, Child-Pugh and Malatack's classifications were used[6,7]. With Child-Pugh clasisfication, of cirrhotic patients, 23 (60.5%) were in group A, six (15.8%) were in group B and nine (23.7%) were in group C. In respect to the Malatack scoring model, 28 (73.7%) were in low risk, four (10.5%) were in moderate risk and six (15.8%) were in high risk groups. After 12-hour fasting, plasma apo A-I, serum cholesterol, total and conjugated bilirubin, albumin and prothrombin time were studied.

For statistical study mean ± standard deviation, Student's t test, Pearson's and Spearman's correlation tests and regression analysis were used.

Results

Mean apo A-I values of cirrhotic, non-cirrhotic and healthy children were 101.0 ± 7.2 mg/dl, 113.0 ± 14.4 mg/dl and 115.1 ± 17.7 mg/dl, respectively. No statistical difference was detected between them ($p > .05$). Cirrhotic children classified according to Child-Pugh and Malatack's classifications were re-evaluated. Results of these two evaluations are shown in Table I.

prothrombin time ($p < .01$, $p < .01$, $p < .01$, $p < .01$, $p < .05$, respectively), but no correlation was found between apo A-I and cholesterol or albumin ($p > .05$ and $p > .05$).

Figures 1 and 2 show the linear regression analysis of apo A-I and Malatack score and of apo A-I and Child-Pugh score.

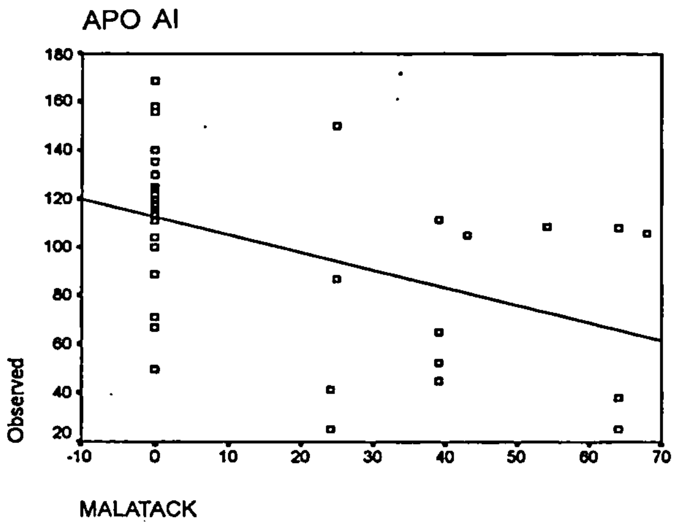

Fig. 1. Regression analysis of apo A-I and Malatack scores.

Table I. Mean Apo A-I Levels and Child-Pugh and Malatack Classifications

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Apo A-I (mg/dl)	n=23	n=6	n=9
	117.4 ± 26.4	80.5 ± 46.1	72.7 ± 34.3
	Low risk	Moderate risk	High risk
Apo A-I (mg/dl)	n=28	n=4	n=6
	109.5 ± 36.6	68.8 ± 20.0	81.8 ± 39.2

Mean apo A-I value was the highest in Child-Pugh A group and was statistically different from Cihld-Pugh B and C groups ($p < .05$ and $p < .001$). The mean apo A-I level was the lowest in the moderate risk group of Malatack's model, and was significantly different from the low risk group ($p < .05$). The mean apo A-I value of six patients who died while awaiting transplantation was 65.2 ± 34.8 mg/dl.

When cirrhotic children were re-evaluated in respect to the presence of cholestasis, mean apo A-I values were 89.0 ± 41.0 mg/dl in the cholestatic group and 117.6 ± 23.2 mg/dl in the non-cholestatis group ($p < .05$).

A negative correlationwas found between apo A-I level and Malatack score, Child-Pugh score, total bilirubin, conjugated bilirubin, and

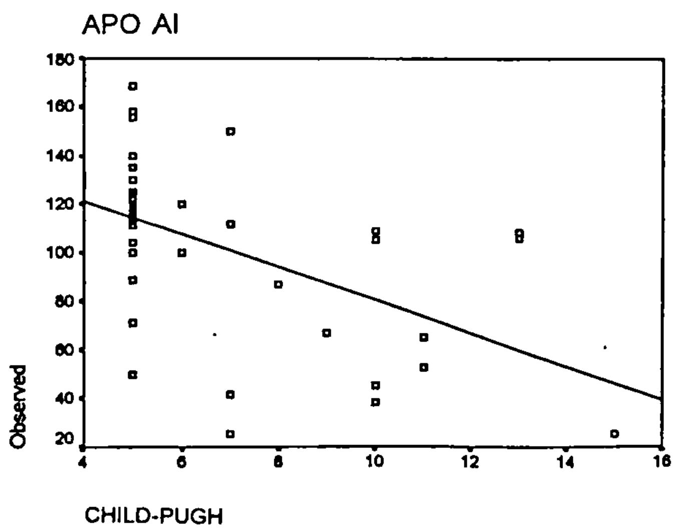

Fig. 2. Regression analysis of apo A-I and Child-Pugh scores.

Regression analysis, showed the following equations.

Apo A-I: 148.5 – (6.8 x Child-Pugh score).

Apo A-I: 112.7 – (0.734 x Malatack score).

With these equations, apo A-I values pairing with cut-off values of Child-Pugh and Malatack stage scores were found. Table II shows the pairing values.

Sensitivity, specificity, and positive predictive and negative predictive values of these cut-off values are shown in Tables III and IV.

Malatack et al.[6] established a prognostic criteria model to predict survival in children with cirrhosis. The four variables with high proportional risk, which included serum cholesterol level, indirect bilirubin level, PTT over 20 seconds, and a positive history of ascites, were placed in a multiplicative exponential model, and this model was used to develop survival curves predictable of survival over a given time[5].

Another widely used prognostic classification for the cirrhotic child is Child-Turcotte, modified by Pugh et al. This model also involves bilirubin, albumin, prothrombin time, and additionally the presence of ascites and encephalopathy[7].

Table II. Apo A-I Values Pairing With Cut-off Values of Child-Pugh and Malatack Staging Scores

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Apo A-I value (mg/dl)	> 101	80-101	< 80
	Low risk	Moderate risk	High risk
Apo A-I value (mg/dl)	> 92	83-92	< 83

Table III. Sensitivity, Specificity, and Positive and Negative Predictive Values of Cut-off Apo A-I Levels for Child-Pugh Classification

Apo A-I	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative pedictive value (%)
> 101 mg/dl for Child-Pugh A	80	57	72	66.6
80-101 mg/dl for Child-Pugh B	20	93	33.3	87.5
< 80 mg/dl for Childh-Pugh C	55.5	84	55.5	84

Table IV. Sensitivity, Specificity, and Positive and Negative Predictive Values of Cut-off Apo lA-I Levels for Malatack Model

Apo A-I	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative pedictive value (%)
> 92 mg/dl for LRG[1]	72	44.4	78.2	36.4
83-92 mg/dl for MRG[2]	30	93.3	0	87.5
< 83 mg/dl for HRG[3]	25	95.4	50	87

[1] Low group.
[2] Moderate risk group.
[3] High risk group.

Discussion

An accurate and informative test of liver function should indicate early in the patient's course when irreversible and potentially fatal changes have occurred. In addition, it should pose no risk to the patient. The standard measurements of hepatic function involve a number of tests, few of which actually measure liver function. Most available tests have poor predictive value until almost complete liver failure has occurred, and none is specific for patients with cirrhoiss[5].

Apo A-I, synthesized in hepatocytes, was measured in serums of cirrhotic adult patients and found to be lower than normal[4,8-11]. Both apo A-I and pro apo A-I converting enzyme activity were found to be lower in adult patients with acute hepatitis and liver cirrhosis than in healthy ones[1,12,13].

Apo A-I has been evaluated according to the prognosis of cirrhosis in only a few studies[2]. Ciccarese et al.[2] studied this parameter in 84 cirrhotic patients and reported a gradual decrease from Child-Pugh A to Child-Pugh B group.

We studied apo A-I in 38 cirrhotic children, and evaluated the results in respect to the routinely used prognostic criteria. Although apo A-I values tended to gradually decrease in the cirrhotic group, we found no statistically significant difference between mean apo A-I values in cirrhotic, non-cirrhotic and healthy children. However, in the cirrhotic group, according to Child-Pugh classification, this decline was more prominent and statistically significant ($p < .05$ and $p < .001$). The non-significant difference between cirrhotic and healthy children was due to the porportionally high case number participating in the Child-Pugh A group, where the mean apo A-I value was non-significantly higher than that of controls (117.4 ± 26.4 and 115.1 ± 17.7, respectively).

When this parameter was evaluated in respect to the scoring model that Malatack et al.[6] established, the mean value was lower in the moderate risk group than in the low risk group ($p < .05$). For a healthy evaluation, this parameter was tested to determine whether it was correlated with widely accepted prognostic criteria such as cholesterol, total and direct bilirubin, prothrombin time, and albumin. By using these correlation tests, we found an inverse correlation between apo A-I and both total and direct bilirubin, and prothrombin time ($p < .01$, $p < .01$, and $p < .05$, respectively). These results were confirmed by non-parametric correlation tests between apo A-I and both Child-Pugh and Malatack scoring models ($p < .01$ and $p < .01$, respectively).

Cholestasis caused low levels of apo A-I; this is consistent with the inverse correlation between bilirubin and apo A-I ($p < .01$). Floren et al.[3] also observed low levels and an inverse correlation with bilirubin levels in cholestatic cirrhotic adult patients. This result may be attributed to the fact that the majority of cholestatic patients were in the Child-Pugh B or C groups. In addition, it is known that apolipoproteins are decreased or absent in very low density lipoprotein (VLDL) particles in cholestasis[14]. This result suggests that a low apo A-I level is also a good indicator of cholestasis.

There is no functional difference between pro and mature apo A-I in respect to LCAT (lecithin-cholesterol acyltransferase) enzyme activation, high density lipoprotein (HDL), and chylomicron interaction[1]. For that reason, it is not clear what kind of lipid metabolism abnormality is caused by that impaired enzyme activity in liver disease. Since some studies revealed that apo A-I catabolism increases two- to four-times normal level, especially in alcoholic hepatitis, it was speculated that low levels found in liver diseases were due to an increase in catabolism rather than to a synthetic disorder[14] In this study, we detected no correlation between apo A-I level and albumin, an indicator of the liver's synthetic capacity. In some studies this correlation has been reported in adults[2,10]. Our finding reveals two speculations: whether apo A-I is a more sensitive indicator of impaired synthesis than albumin, and whether cirrhosis really causes increased catabolism of apo A-I. Apo A-I and A-II, in the plasma of patients with liver disease, often show complete dissociation and lose their binding capacity. It is possible that this dissociation is a major reason for their accelerated catabolism, and this may well result from a disturbed generation of mature HDL from nascent HDL[14]. In liver diseases, HDL fraction not only shows decreased concentrations of apo A-I and A-II, but also a marked increase in apo e; the same picture is defined for familial LCAT deficiency[14].

To date, no study has established a cut-off value for apo A-I predicting poor prognosis. We tried to establish this value using routinely accepted scoring models, Malatack's and Child-Pugh classifications. With the equations we found by regression analysis, we detected the paired values with cut-off scores of these two parameters. In addition, we calculated the positive and negative predictive values, specificity, and sensitivity. We observed that the specificity and negative predictive values we found were becoming higher in worse prognoses. This means that a low apo A-I level is more specific to end-stage liver disease and less specific to liver injury scored as Child-Pugh A or low risk. This result can be confirmed by the non-significant difference between all cirrhotic patients, consisting mainly of Child-Pugh A patients, and healthy children. Consequently, a low apo A-I level is not a laboratory marker of cirrhosis, but an indicator of poor prognosis in cirrhotic patients.

To the best of our knowledge, apo A-I has not been used routinely in gastroenterology clinics for prognostic purposes in cirrhotic patients, especially in pediatric age groups. This study is a first-step investigation for determining the cut-off values of apo A-I predicting poor prognosis. This routinely used parameter may be employed in prognostic staging models. We believe that with long-term studies, these cut-off values can be confirmed or modified.

REFERENCES

1. Oseb H, Sakai H, Satoh M, Sakamoto S, Koga S, Nawata H. Decreased proapolipoprotein A-I converison. Clin Chim Acta 1990; 189: 303-312.
2. Ciccarese M, Tonolo G, Brizzi P, et al. Serum apolipoprotein (a) concentrations and Apo (a) phenotypes in patients with liver cirhosis. Am J Gastroenterol 1998; 93: 1505-1509.
3. Floren CH, Gustafson A. Apolipoprotein A-I, A-II and E in cholestatic liver disease. Scand J Clin Lab Invest 1995; 45: 103-108.
4. Vergani C, Trovato G, Pietrogrande M,m Crocchiolo P, Dioguardi N. Behaviour of total lipids, cholesterol, lipoproteins and apolipoprotein A in the blood of subjects with acute hepatitis and chronic hepatopathy. Minerva Med 1978; 69: 2081-2094.
5. Hardy SC, Kleinman RE. Cirrhosis and chronic liver failure. In: Suchy FJ (ed.) Liver Disease in Children. St. Louis: Mosby; 1994: 214-248.
6. Malatack JJ, Schaid DJ, Urbach AH, et al. Choosing a paediatric recipient for orthotopic liver transplantation. J Pediatr 1987; 111: 479-489.
7. van Dam GM, Gips CH, Reisman Y, et al. MAjor clinical events, signs and severity assessment scores related to actual survival in patients who died from primary biliary cirrhosis. A long-term historical cohort study. Hepatogastroenterology 1999; 46: 108-115.
8. Suehiro T, Yamamoto M,m Yoshida K, Ohno F. Increase of plasma pro apolipoprotein A-I in patients with liver cirrhosis and its relationship to circulating high-density lipoproteins 2 and 3. Clin Chem 1993; 39: 60-65.
9. Jorge AD, Ponce G, Milutin C, et al. Importance of apolipoproteins A-I and B in acute viral hepatitis and hepatic cirrhosis. Acta Gastorenterol Latinoam 1986; 16: 39-46.
10. Nayak SS, Ramani A, Kamath SS, Kundaje GN, Aroor AR. Serum apoproteins A and B and the lecithin: cholesterol acyl transferase activities in liver cirrhosis and hepatic coma patients. Biochem Med Metab Biol 1988; 40: 299-304.
11. Matsuura T, Koga S, Ibayashi H. Increased proportion of pro apolipoprotein A-I in HDL from patients with liver cirrhosis and hepatitis. Gastroenterol Jpn 1988; 23: 394-400.
12. Malmendier CL, Mailier EL, Amerijckx JP, Fischer ML. Plasma levels of apolipoproteins A-I, A-II and B in alcoholism. Relation to the degree of histological liver damage, and to liver function tests. Hepatogastroenterology 1983; 30: 236-239.
13. Paynard T, Abella A, Pignon JP, Naveau S, Leluc R, Chaput JC. Apolipoprotein A-I and alcoholic liver disease. Hepatology 1986; 6: 1391-1395.
14. Siedel D. Lipoproteins in liver disease. J Clin Chim Biochem 1987; 25: 541-551.