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# Alpha-2-Macroglobulin and Hepatic Fibrosis
## Diagnostic Interest

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Alpha-2-macroglobulin ($A_2M$) is a proteinase inhibitor. Cells synthesizing $A_2M$ are in first-order hepatocytes and in second-order activated Ito cells (in culture starting at day 4–5 after seeding). This study was undertaken in 525 alcoholic patients with different histological stages of alcoholic liver disease to assess if the $A_2M$ could improve the diagnostic value of PGA index for detection of cirrhosis or fibrosis among drinkers, particularly in patients without clinical symptoms of liver failure and portal hypertension, and to assess the specific correlation of serum $A_2M$ with the score of liver fibrosis adjusted for steatosis and alcoholic hepatitis and thereafter adjusted for GGT, PT, and ApoA1, the three components of the PGA index. In 525 alcoholic patients, we have demonstrated the independent diagnostic value of $A_2M$. The predictive values of the weighted score, using linear discriminant function combining PT, GGT, ApoA1 and $A_2M$ of the PGAA score and of the PGA score were assessed in a training step and validated in a second step. Then, 316 alcoholic clinically asymptomatic patients were studied. In these patients, the discriminant function permitted correct classification of 72% of patients. The PGAA index had comparable diagnostic value with 70% of patients correctly classified. On the other hand, the PGA index including only PT, GGT, and ApoA1 had classified correctly less patients (65%) than the discriminant function and the PGAA index ($P < 0.01$). For a value of 7, PGAA had 79% specificity and 89% sensitivity for the diagnosis of cirrhosis. $A_2M$ was positively correlated with the grade of fibrosis ($r = 0.39$ $P < 0.01$). The correlation persisted whatever the degree of steatosis and the degree of alcoholic hepatitis and after adjustment for GGT, PT, and ApoA1. When liver biopsy is not possible, PGAA could be useful for the diagnosis of asymptomatic cirrhosis among drinkers.

**KEY WORDS:** alpha-2-macroglobulin; fibrosis; alcoholic cirrhosis; drinkers; diagnosis.

Several reports have shown that serum levels of some extracellular matrix proteins such as type III procollagen aminopeptide (PIIIp) (1), type IV collagen (2), laminin (3), serum levels of the subunit of fibronectin receptor (4), and apolipoprotein A1 (ApoA1) (5) may be good markers of hepatic fibrosis. Nevertheless, the diagnostic value of each single marker is not accurate enough to detect patients with fibrosis or cirrhosis. Recently, it was reported that a simple biological index, which combines prothrombin time (PT), serum gamma-glutamyltranspeptidase (GGT), and ApoA1, was useful to identify high-risk subjects for severe liver disease (6).

Alpha-2-macroglobulin ($A_2M$) is a proteinase inhibitor characterized by its wide inhibitory spectrum to proteinases (7). Ito cells are supposed to play a major role in the production of interstitial

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TABLE 1. PGAA INDEX FOR DIAGNOSIS OF ALCOHOLIC LIVER DISEASE IN DRINKERS

| *Score according to degree of abnormality* | *PT (% of control)* | *GGT (IU/liter)* | *ApoA1 (mg/dl)* | *$A_2M$ (g/liter)* |
|---|---|---|---|---|
| 0 | ≥80 | <20 | ≥200 | <1.25 |
| 1 | 70–79 | 20–49 | 175–199 | 1.25–1.74 |
| 2 | 60–69 | 50–99 | 150–174 | 1.75–2.24 |
| 3 | 50–59 | 100–199 | 125–149 | 2.25–2.74 |
| 4 | <50 | ≥200 | <125 | ≥2.75 |

protein such as collagens or fibronectin (8), and it was demonstrated that Ito cells of rat liver are also able to express the $A_2M$ gene in primary cultures (9). Thus one can speculate that increased synthesis of $A_2M$ can inhibit the catabolism of matrix proteins and enhance fibrotic processes in the liver.

This prospective study of serum $A_2M$ was undertaken in a population of alcoholic patients with different histological stages of alcoholic liver disease to assess if $A_2M$ could improve the diagnostic value of the PGA index for detection of cirrhosis or fibrosis, particularly in patients without clinical symptoms of liver failure and portal hypertension, and to assess in these patients the specific correlation of serum $A_2M$ with the score of liver fibrosis adjusted for steatosis, and alcoholic hepatitis and thereafter adjusted for GGT, PT, and ApoA1, the three components of the PGA index (6).

## MATERIALS AND METHODS

### Patients

Patients included in the study were admitted to the hepatogastroenterology units of the Antoine Béclère Hôspital in Clamart France, for alcoholism or alcoholic liver disease. To be considered for inclusion, patients had to have drunk at least 50 g of alcohol per day during the previous five years.

The protocol of this prospective study included serum $A_2M$ determination, ApoA1 measurements, and serum liver tests (including PT and GGT) in all alcoholics within two days after admission and a liver biopsy within two weeks. In all 525 patients were included; 50 patients were excluded because biopsy was refused. Association with severe non liver disease led to the exclusion of 101 patients because this alone could alter serum lipoprotein or liver tests. The clinical characteristics of the patients included details of age, sex, alcohol consumption, smoking, and nutritional parameters. These nutritional parameters measured within the two days after admission were upper arm fat and upper arm muscle areas expressed in percentage of the standard values of age- and sex-specific 50th percentile and the weight expressed in percentage of ideal body weight calculated by the Lorentz formula. The patients were questioned about their alcohol consumption by a resident using a specific questionnaire. Patient's families were also interviewed if possible. Thereafter, each questionnaire was checked by an assistant in the presence of the patient.

### Biology

PT, GGT activity, ApoA1, and $A_2M$ concentration were measured the day after admission. Each variable was given a value of 0, 1, 2, 3, or 4, respectively, for increasing abnormality, and the values added up over the four variables for each patient. Thus, the total score ranged between 0 to 16. This resulted in the PGAA index (Table 1). Apolipoprotein A1 was measured by electroimmunoassay using prepared plates (Sebia, Issy-les-Moulineaux, France). Details of the method have been given elsewhere (10). Serum GGT activity was determined using the Szasz assay (11) and expressed in international units per liter. The concentration of $A_2M$ was determined in serum samples by laser immunonephelometry using a Behring Nephelometer Analyzer (12). The reagent was a rabbit antiserum against human $A_2M$. The serum concentration of $A_2M$ was expressed in grams per liter.

### Histology

All patients underwent percutaneous liver biopsy with a 1.8-mm diameter needle (Hepafix; B. Braun, Melsungen, Germany). Liver biopsies were read independently by two pathologists. The specific questionnaire used has been described and validated elsewhere (13). Morphological criteria were those accepted internationally (14). We have used histologic scores (scores of steatosis, fibrosis, and alcoholic hepatitis) based on a semiquantitative assessment of lesion (15). According to this assessment of pathologic features, 177 patients had cirrhosis, and 49 patients had alcoholic hepatitis considered significant (ie, a score of alcoholic hepatitis ≥2 on a scale ranging from 0 to 6) without cirrhosis. One hundred fifteen patients had fibrosis considered significant (ie, a score of fibrosis ≥2 on a scale ranging from 0 to 8) without alcoholic hepatitis; 184 patients had normal liver biopsy, or minimal changes, for example, only steatosis or fibrosis considered minor (ie, a score equal to 1) or alcoholic hepatitis considered minor (ie, a score equal to 1).

### Statistical Methods

**Descriptive Analysis.** Quantitative variables were compared using an analysis of variance with Bonferroni's test. Qualitative variables were compared utilizing the $\chi^2$ test and Yates' corrected $\chi^2$ test.

**Diagnostic Analysis.** The event to be predicted first was liver fibrosis, which included fibrosis, alcoholic hepatitis,

TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS

| | *Training period* | *Validation period* | P |
|---|---|---|---|
| Number of subjects | 222 | 303 | |
| Age* | 49 ± 12 | 48 ± 11 | NS |
| Men (%) | 74 | 73 | NS |
| Alcohol intake during last 5 years (g/day) | 120 ± 68 | 124 ± 87 | NS |
| Mean duration of alcoholism (year) | 22 ± 13 | 21 ± 11 | NS |
| Cigarette smokers (%) | 70 | 74 | NS |
| Ascites (%) | 16 | 21 | NS |
| Encephalopathy (%) | 6 | 8 | NS |
| Digestive hemorrhage (%) | 10 | 12 | NS |
| Ideal body weight (%) | 104 ± 20 | 105 ± 20 | NS |
| Upper arm fat area (%) | 56 ± 33 | 57 ± 41 | NS |
| Upper arm muscle area (%) | 82 ± 25 | 83 ± 30 | NS |
| Liver histology | | | |
| Normal or minimal changes | 96 | 88 | |
| Fibrosis or alcoholic hepatitis | 56 | 108 | <0.01 |
| Cirrhosis | 70 | 107 | |

*Means are expressed with standard deviation.

and cirrhosis and, second, cirrhosis with or without alcoholic hepatitis.

This study was conducted in three steps: first a training step (the first 36 months) and second a validation step (the last 36 months). The independent diagnostic value of $A_2M$ was demonstrated using stepwise discriminant analysis. Using linear discriminant function, we assessed the percentage of patients correctly classified by a weighted score combining PT, GGT, ApoA1, $A_2M$; by the simple PGAA score; and by the PGA score. The predictive values of the weighted score using linear discriminant function, the PGAA score, and the PGA score were validated in the second step.

Because in asymptomtic patients, cirrhosis is not easy to diagnose and needs histological confirmation, a third step concerns only patients without clinical symptoms of liver failure and portal hypertension. On the day of admission 316 asymptomatic patients were defined as drinkers without jaundice, ascites, encephalopathy, or digestive hemorrhage. In these patients, the predictive value of the score using the linear discriminant function of PT, GGT, ApoA1, and $A_2M$ was also compared with the simple PGAA score and PGA score. The diagnostic value of the PGAA index has been assessed measuring the predictive value of four classes of PGAA scores (0–3, 4–7, 8–11, 12–16) in the diagnosis of three alcoholic liver diseases: (1) normal liver or with minimal changes (as defined above), (2) noncirrhotic fibrosis with or without alcoholic hepatitis, and (3) cirrhosis.

The diagnostic value of the PGAA score was estimated using a receiver operating curve that plots true positive rates against false positive rates, first for the diagnosis of liver fibrosis, which included fibrosis, alcoholic hepatitis, and cirrhosis, and second for the diagnosis of cirrhosis, which included cirrhosis with or without alcoholic hepatitis.

**Relationships Between $A_2M$ and Scores of Fibrosis in Asymptomatic Patients.** The independent correlation of $A_2M$ to the score of fibrosis, adjusted for the score of steatosis and the scores of alcoholic hepatitis, and the independent correlation of $A_2M$ to the score of fibrosis, adjusted for PT, GGT, and ApoA1, was assessed by two regression analyses with partial correlation analysis.

## RESULTS

### Diagnostic Analysis

**First Step: Training Step.** In all, 222 patients were studied. Their characteristics are given in Tables 2 and 3. In the discriminant analysis combining PT, GGT, ApoA1, and $A_2M$, $A_2M$ had a significant independent discriminant value ($P < 0.001$). The discriminant function combining these four variables permitted us correctly classify 71% of patients. The simple PGAA index, which is easier to use than the discriminant function, had comparable diagnostic value with 71% of patients correctly classified. On the other hand, the PGA index including only PT, GGT, and ApoA1, classified fewer patients correctly (65%) than the discriminant function ($P < 0.01$) and the PGAA index ($P < 0.02$).

TABLE 3. BIOLOGICAL CHARACTERISTICS OF PATIENTS*

| | *Training period* | *Validation period* | P |
|---|---|---|---|
| Number of subjects | | | |
| PT | 84 ± 18 | 84 ± 19 | NS |
| GGT (IU/liter) | 188 ± 280 | 200 ± 257 | |
| TSB† (μmol/dl) | 2.8 ± 4.1 | 3.4 ± 5.4 | |
| ApoA1 (mg/dl) | 159 ± 63 | 136 ± 57 | <0.01 |
| $A_2M$ (g/liter) | 1.8 ± 0.5 | 2.2 ± 0.7 | <0.01 |
| PGA (range 0–12) | 5.1 ± 3 | 6 ± 2.5 | <0.01 |
| PGAA (range 0–16) | 6.7 ± 3.4 | 8.3 ± 3 | <0.01 |

*Means are expressed with standard deviation.
†Total serum billrubin.

TABLE 4. CLINICAL CHARACTERISTICS OF ASYMPTOMATIC PATIENTS

| *Characteristics* | *Normal or minimal changes* | *Fibrosis or alcoholic hepatitis* | *Cirrhosis* |
|---|---|---|---|
| Number of subjects | 207 | 64 | 45 |
| Age (mean ± SD | 46 ± 12 a* | 48 ± 11 | 53 ± 11 b |
| Men (%) | 166 (90) | 48 (75) | 32 (71) |
| Alcohol Intake during last 5 years (g/day, mean ± SD) | 134 ± 95 | 125 ± 89 | 132 ± 63 |
| Mean duration of alcoholism (year, mean ± SD) | 20 ± 12 c | 22 ± 12 | 26 ± 13 d |
| Cigarette smokers (%) | 52 (25) | 20 (31) | 14 (31) |
| Idean body weight (%) | 100 ± 18 | 104 ± 24 | 103 ± 18 |
| Upper arm fat area (%) | 62 ± 43 | 64 ± 47 | 50 ± 27 |
| Upper arm muscle area (%) | 82 ± 21 | 80 ± 25 | 86 ± 20 |

*Significant difference with cirrhosis: a, $p < 0.01$; c, $P < 0.05$. Significant difference with normal or minimal change: b, $P < 0.01$; d, $P < 0.05$.

**Second Step: Validation Step.** In all, 303 patients were studied. Their characteristics are given in Tables 2 and 3. In the discriminant analysis $A_2M$ had also a significant independent discriminant value ($P < 0.001$). The discriminant function combining the four variables permitted us to correctly classify 67% of patients, which was not significantly different from the 71% obtained in the training step but was significantly different from the 61% obtained with the PGA score ($P < 0.001$) in this validation step.

**Third Step: Diagnostic Analysis in Asymptomatic Drinkers.** In all, 316 patients were studied. Their characteristics are given in Tables 4 and 5. In the discriminant analysis combining PT, GGT, ApoA1, and $A_2M$, $A_2M$ had a significant independent discriminant value ($P < 0.001$). The discriminant function combining these four variables permitted us to correctly classify 72% of patients. The simple PGAA index, which is easier to use than the discriminant function, had comparable diagnostic value with 70% of patients correctly classified. On the other hand, the PGA index including only PT, GGT, and ApoA1 had classified fewer patients correctly (65%) than the discriminant function and the PGAA index ($P < 0.01$). The positive predictive value of the PGAA index for the diagnosis of alcoholic liver disease is given Table 6. No patient with score ≤3 had cirrhosis and no patient with score ≥12 had normal or minimal changes. Details of true positive and false positive rates according to the PGAA score for the diagnosis of fibrosis (including fibrosis, alcoholic hepatitis, and cirrhosis) and for diagnosis of cirrhosis (with or without alcoholic hepatitis) are given in Figures 1 and 2. For a value of 6, PGAA had 77% specificity and 75% sensitivity for diagnosis of fibrosis. For a value of 7, PGAA had 79% specificity and 89% sensitivity for the diagnosis of cirrhosis.

### Relationships Between $A_2M$ and Scores of Fibrosis in Asymptomatic Patients

**Correlation with Total Amount of Fibrosis Semiquantitatively Assessed in 316 Patients.** Values of $A_2M$ according to the semiquantitative score of fibrosis are given in Table 7. There was a progressive increase of $A_2M$ according to the grade of fibrosis. $A_2M$ concentration reached a minimum in patients with a fibrosis score of 0 and reached a maximum in patients with a fibrosis score of 6. Simple correlation analysis shows that $A_2M$ was

TABLE 5. BIOLOGICAL CHARACTERISTICS OF ASYMPTOMATIC PATIENTS*

| *Characteristics* | *Normal or minimal changes* | *Fibrosis or alcoholic hepatitis* | *Cirrhosis* |
|---|---|---|---|
| Number of patients | 207 | 64 | 45 |
| PT | 96 ± 7b,e† | 88 ± 13a,e | 72 ± 16a,b |
| GGT (IU/liter) | 99 ± 107b,e | 189 ± 242a | 227 ± 170a |
| ApoA1 (mg/dl) | 220 ± 70 | 200 ± 90 | 140 ± 60a,e |
| $A_2M$ (g/l) | 1.7 ± 0.6e | 1.9 ± 0.6e | 2.6 ± 0.8a,b |
| PGA (range 0–12) | 2.8 ± 1.7b,e | 4.5 ± 2.3a,e | 7.3 ± 2.4a,b |
| PGAA (range 0–16) | 5.5 ± 2b,e | 6.9 ± 2.4a,f | 8.4 ± 2.5a,d |

*Means are expressed with standard deviation.
†Significant difference with normal or minimal changes: a, $P < 0.001$. Significant difference with fibrosis or alcoholic hepatitis: b, $P < 0.001$; c, $P < 0.01$; d, $P < 0.05$. Significant difference with cirrhosis: e, $P < 0.001$; f, $P < 0.05$.

TABLE 6. POSITIVE PREDICTIVE VALUES OF PGAA INDEX FOR DIAGNOSIS OF ALCOHOLIC LIVER DISEASE IN ASYMPTOMATIC PATIENTS

| PGAA value | Normal or minimal changes | | Fibrosis or alcoholic hepatitis | | Cirrhosis | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| 0–3 | 88 | 93 | 7 | 7 | 0 | 0 | 95 | 100 |
| 4–7 | 104 | 69 | 40 | 26 | 7 | 5 | 151 | 100 |
| 8–11 | 15 | 26 | 16 | 28 | 26 | 46 | 57 | 100 |
| 12–16 | 0 | 0 | 1 | 8 | 12 | 92 | 13 | 100 |
| Total | 207 | | 64 | | 45 | | 316 | 100 |

positively correlated with the grade of fibrosis ($r$ = 0.39, $P < 0.001$).

**Correlation with Fibrosis Adjusted for Steatosis and Alcoholic Hepatitis and for GGT, PT, and ApoA1.** In the univariate analysis, the score of alcoholic hepatitis was correlated with $A_2M$ significantly and positively ($r$ = 0.20) and with the score of fibrosis ($r$ = 0.48).

The score of steatosis was significantly and positively correlated with the score of fibrosis ($r$ = 0.20) but was not correlated with $A_2M$. In the multivariate regression, the correlation between $A_2M$ and the score of fibrosis persisted whatever the score of alcoholic hepatitis and the score of steatosis ($r$ = 0.28, $P < 0.001$).

In the univariate analysis PT was significantly and negatively correlated with $A_2M$ ($r$ = 0.39) and with the score of fibrosis ($r$ = 0.60).

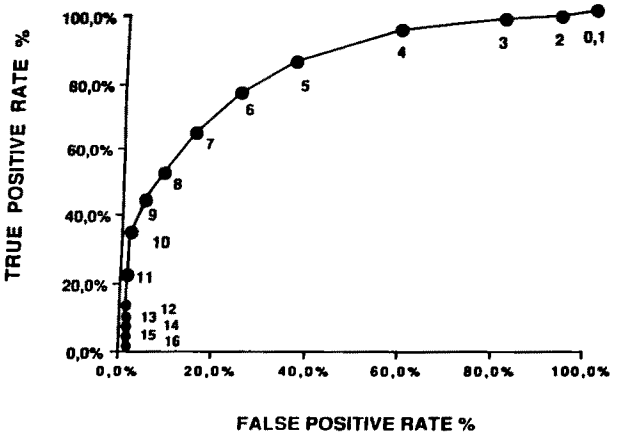


**Fig 1.** Receiver operating curve of PGAA index for the diagnosis of liver fibrosis, which included fibrosis, alcoholic hepatitis, or cirrhosis. The ordinate represents the true positive rate while the abscissa represents the false positive rate for each score of PGAA. This score fluctuates between 0 to 16 and the values are noted along the curve. For example, for a score of 6, the rate of true positive (sensitivity) is 75% and the rate of false positive (1 − specificity) is 23%.

TABLE 7. $A_2M$ CONCENTRATIONS IN DRINKERS ACCORDING TO FIBROSIS SCORE IN ASYMPTOMATIC PATIENTS

| Fibrosis score | Patients (N) | $A_2M$ (g/liter, mean ± SD) |
|---|---|---|
| 0 | 158 | 1.69 ± 0.6 a,b* |
| 1 | 49 | 1.78 ± 0.6 a,b |
| 2 | 12 | 1.90 ± 0.6 |
| 3 | 7 | 2.08 ± 0.7 |
| 4 | 11 | 2.08 ± 0.9 |
| 5 | 24 | 2.04 ± 0.7 |
| 6 | 32 | 2.45 ± 0.8 |
| 7 | 23 | 2.37 ± 0.8 |

*a: Significant difference with score 6 ($P < 0001$); b: significant difference with score 7 ($P < 0.001$).

GGT was significantly and positively correlated with $A_2M$ ($r$ = 0.20) and the score of fibrosis ($r$ = 0.29).

ApoA1 was negatively and significantly correlated with the score of fibrosis ($r$ = 0.30) but was not correlated with $A_2M$.

In the multivariate regression, the correlation between $A_2M$ and the score of fibrosis persisted after adjustment for GGT, PT, and ApoA1 ($r$ = 0.17 $P <$ 0.005).

## DISCUSSION

Numerous reports have shown an increase in the levels of $A_2M$ and a reduction of other proteins of hepatic origin in the serum of patients with cirrhosis of the liver compared with normal subjects (16–18). Although the hepatocytes are of major importance for the synthesis and the turnover of $A_2M$ (19), we have thought that this strikingly different behavior of $A_2M$ from the other serum proteins of hepatic origin could be of some diagnostic interest in the case of alcoholic hepatic fibrosis and cirrhosis. For this reason, and because the PGA index is the best

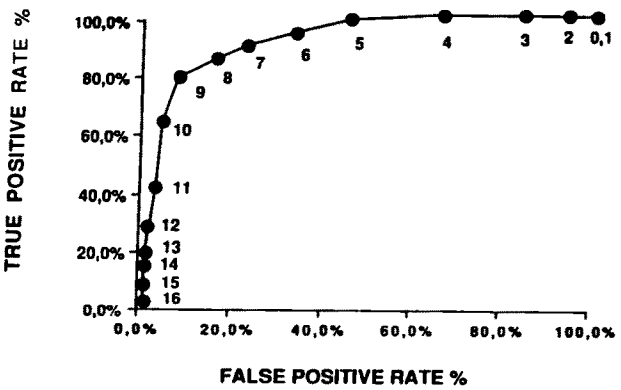


**Fig 2.** Receiver operating curve of PGAA index for the diagnosis of cirrhosis, which included cirrhosis with or without alcoholic hepatitis.

index ever assessed for detection cirrhosis among drinkers (6), we have studied if $A_2M$ could improve the diagnostic value of the PGA index for detection of cirrhosis or fibrosis among drinkers. Effectively, in the training step, the 71% of patients correctly classified by a weighted score combining PT, GGT, ApoA1, and $A_2M$ using linear discriminant function and by the PGAA score were significantly different from the 65% obtained with the PGA score. In the validation step, $A_2M$ had also an independent diagnostic value and the linear discriminant function improved also significantly the diagnostic value of the PGA score. Nevertheless, although not significantly different, the percentage of patients correctly classified by the weighted score was less than in the training step (67% versus 71%). This result is probably explained by differences between the patients of the two periods. The patients of the validation step had less normal or minimal changes of liver and had more fibrosis ($P < 0.01$) (for this reason, $A_2M$, PGA score, and PGAA score were significantly higher in patients of the second period and ApoA1 was significantly lower). The linear discriminant function correctly classified normal or minimal changes of liver and cirrhosis better than fibrosis. An asymptomatic population is the best sample for screening purposes and, therefore, we have particularly studied this group of patients. For detection of asymptomatic cirrhosis among drinkers, the PGAA index at a cutoff of 7 has 79% specificity and 89% sensitivity.

Although the development and refinement of many new techniques aid in the diagnosis of liver disease, liver biopsy is the procedure of choice for proving the diagnosis of liver disease, but one must weigh the potential gains against the risks. The procedure is safe, but it must be carried out only in institutions in which physicians are experienced with the technique, are aware of the risk entailed, and will follow the patients closely for at least 24 hr after the procedure is completed. When these conditions are not present, PGAA could be useful for the diagnosis of asymptomatic cirrhosis among drinkers. Thus, we have investigated the correlation between $A_2M$ and the amount of liver fibrosis. Hepatocellular necrosis is followed by fibrosis and cirrhosis, caused by an increase in collagen synthesis and its deposition. The increase in collagen synthesis results from both an increase in the number of collagen-producing cells and an increase of collagen synthesis per cell. Besides collagen, other components of the extracellular matrix, such as fibronectin and laminin, contribute to the formation of fibrosis and cirrhosis (20). The major producers of these extracellular matrix proteins are Ito cells (liver fat-storing cells), fibroblasts, hepatocytes, and endothelial cells (8). The $A_2M$ gene was demonstrated in cultured Ito cells beginning at day 4–5 after seeding (9), and transformed fat-storing cells of rat liver bind and internalize activated $A_2M$ (21). These observations suggest that $A_2M$ could play an important role for collagen metabolism in liver diseases. Furthermore, transforming growth factor β1 (TGF-β1) is capable of activating lipocyte cells to become fibrogenic (22) and might limit proteolysis by stimulating synthesis of antiproteases both locally and systemically (23). Recently, Bachem et al presented data that suggest positive and negative autocrine loops including TGF-β1 and $A_2M$ in the relation of proteoglycan synthesis of activated perisinusoidal lipocytes (myofibroblast like cells) isolated from normal rat livers (24).

This study demonstrates that in alcoholic patients the increase of $A_2M$ was correlated to the amount of fibrosis and established that $A_2M$ is a marker of hepatic fibrosis. Necroinflammatory disorders of the liver such as acute alcoholic hepatitis (AAH) are similar in some aspects to the host acute-phase response (25). During inflammation and tissue injury, there is an increase in the plasma concentration of several proteins; however, in contrast to $A_2M$ of a number of other animal species such as the rat, human $A_2M$ is not an acute-phase reactant (26). Moreover, in this study the increase of $A_2M$ was correlated with the amount of fibrosis, and this correlation persisted after adjustment for the score of steatosis and alcoholic hepatitis. Thus, our results do not support that liver cell necrosis is sufficient to explain the increase of $A_2M$ in alcoholic patients. $A_2M$ contributes to the control of coagulation and fibrinolysis, but the correlation between $A_2M$ and the score of fibrosis also persisted after adjustment for PT. Furthermore, although $A_2M$ is considered to be a physiological plasmin inhibitor, $A_2M$ does not seem to play a role in enhancing fibrinolysis in patients with cirrhosis (27). $A_2M$ is also significantly correlated with the score of fibrosis, whatever the values of the three components of the PGA index, GGT, PT, and ApoA1.

In conclusion, $A_2M$ is a marker of hepatic fibrosis, which probably explains the interest in it for the diagnosis of hepatic fibrosis and particularly of hepatic cirrhosis.

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