MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 1194-1199
DOI: 10.12659/MSM.893350

Received: 2014.12.19
Accepted: 2015.03.20
Published: 2015.04.27

Low Serum Levels of Alpha$_1$ Anti-trypsin (α_1-AT) and Risk of Airflow Obstruction in Non-Primary α_1-AT-Deficient Patients with Compensated Chronic Liver Disease

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Programa E015 – Investigación Científica y Tecnológica, ISSSTE

Background: Alpha$_1$ anti-trypsin (α_1-AT), a serine protease inhibitor synthesized in the liver, is a major circulating antiprotease that provides defense against proteolytic damage in several tissues. Its deficiency is associated with airflow obstruction. The present study aimed to explore the role of α_1-AT as a biomarker of airflow performance in chronic liver disease (CLD).

Material/Methods: Serum α_1-AT levels and lung function (spirometry) were evaluated in non-primary α_1-AT-deficient, alcoholic CLD patients without evident respiratory limitations.

Results: Thirty-four patients with airflow obstruction (n=11), airflow restriction (n=12), and normal airflow (n=11, age-matched controls) were eligible. α1-AT was decreased in the airflow obstruction group. ROC-cutoff α_1-AT=24 mg/dL effectively discriminated airflow obstruction (AUC=0.687) and was associated with a 10-fold higher risk (p=0.0007).

Conclusions: Lower α_1-AT increased the risk of airflow obstruction in CLD patients without primary α_1-AT deficiency.

MeSH Keywords: Enzyme-Linked Immunosorbent Assay • Lung Diseases • Lung Diseases, Obstructive • Spirometry

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893350

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Background

Pulmonary disorders such as chronic obstructive pulmonary disease (COPD), hepatopulmonary syndrome, and portopulmonary syndrome occur frequently in patients with chronic liver disease (CLD), worsening the clinical prognosis [1]. Some airflow dysfunction in CLD patients is due to the airway inflammation resulting from bacterial translocation coupled with the impaired phagocytosis in the liver [2–4]. Research on new non-invasive biomarkers predicting pulmonary dysfunction in CLD patients would help identify special at-risk populations and establish early preventive measures.

Alpha$_1$ anti-trypsin (α_1-AT) is a serpin secreted from human hepatocytes, other epithelial cells, and monocytes. It is involved in the inflammatory response, whereas low serum levels of α1-AT or a deficient function are associated to airflow obstruction [5]. Recently, α_1-AT and α_1 proteins have been recognized as useful markers for prognosis stratification of heart failure patients [6]. However, there are conflicting data regarding the role of α_1-AT in severity of liver damage [7].

This study was designed to determine serum levels of α_1-AT in patients with CLD, with or without airflow obstruction, to estimate whether it may be a useful biomarker for airflow complications in this population.

Material and Methods

This study was planned as an observational, cross-sectional, descriptive design. The study included patients between 18 and 70 years old, with alcoholic-etiology CLD scored Child-Pugh B (score 7–9) and C (score >10). Patients were further divided into groups of airflow obstruction or airflow restriction according to spirometry performance; age-matched normal airflow controls were included for comparison.

Patients were non-smokers and were not known to have primary deficiency of α_1-AT, based on serum levels of α_1-AT as well as the absence of suggestive history of pulmonary dysfunction in the patients and their parents.

Patients were excluded if they had been exposed to potential risk of lung damage such as biomass burning, prior diagnosis of COPD, hepatic encephalopathy, and mechanical respiratory limitations like ascites, atelectasis, pneumonia, or bronchial asthma. Current pulmonary complications were diagnosed during hospitalization in Medical Units from the Health Service Department, Federal District, Mexico from November 2013 to March 2014. This study was designed and conducted according to the Declaration of Helsinki and was approved by the Institutional Ethics Committees. All patients chose to participate in this research through a signed written informed consent.

Clinical information was acquired through a questionnaire; biochemical parameters, including blood gas analysis, were obtained by routine automated clinical tests analyzed in a Beckman Coulter automated Olympus AU680. The presence of hepatopulmonary syndrome was assessed by orthodeoxia test, defined as a decrease in oxygen saturation greater than 5% or greater decrease in PaO_2 at 4 mmHg passing from supine to upright, in addition to dyspnea, cyanosis, or platypnea.

Determination of serum α_1-AT was performed as follows: a total of 5 mL of blood was collected in a tube without anticoagulant; serum was separated by centrifugation. The sample was kept frozen at -20°C until final processing within 4 weeks. Concentration of α_1-AT was determined with a quantitative immunoassay (Alpha-1-Antitrypsin AA2471 test Randox, Antrim, UK; using a Vitalab Selectra II/E/Flexor analyzer) following manufacturer instructions, which include a combination of patient sera with a buffer containing antibody specific for α_1-AT. Formation of immune complexes modifies the turbidity, the extent of which is measured as the amount of light absorbed at 340 nm. A standard curve was constructed to correlate and estimate the concentration of α_1-AT.

Patient airflow capacity was estimated by standard spirometry using the MicroMedical Spiro-USB Spirometer (Cardinal Health Ltd, Kent, UK) and analyzed with appropriate software (Cardinal Health, Kent UK) and working according to American Thoracic Society / European Respiratory Society (ATS/ERS) standards. Briefly, the patient was asked to sit in a chair with fixed armrests, with the chest upright and the head slightly elevated. A nose clip and mouthpiece were attached to the teeth, and lips were sealed. The patient was instructed to perform a rapid and complete inhalation followed by exhalation maximum sustained effort. ATS/ERS criteria for blow acceptability, repeatability and reproducibility were used. Largest value of FEV_1 and FVC were selected from at least 3 expiratory maneuvers, and bronchial obstruction was considered when FEV_1/FVC was lower than 70% of the predicted value, which also coincided with values below the 5th percentile of the FEV_1/FVC values from age-matched healthy volunteers.

Statistical analysis was performed using summary measures as median and quartiles for clinical and demographic variables. Kolmogorov-Smirnoff test was performed to determine the pattern of distribution of variables. For the inferential analysis, ANOVA and t-test were used to evaluate mean differences, as well as Pearson correlation analysis. Receiver operating characteristics analysis was used to evaluate cutoff value for α_1-AT and area under the curve (AUC) to compare the diagnostic ability. Likelihood of association between low serum

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Table 1. Clinical-demographic characteristics of the study population.

	Normal airflow (n=11)		Airflow obstruction (n=11)		Airflow restriction (n=12)		*p*
	Median	Q25-75	Median	Q25-75	Median	Q25-75	
Age (years)	47.0	38–55	56.0	52–66	53.5	46–59	0.08
Child-Pugh Score	7	7–9	10	8–12	9	7–11	0.01*
TB (mg/dL)	2.7	1.2–4.8	4.4	3.6–16.7	2.6	1.9–11.4	0.46
Albumin (mg/dL)	2.4	2.0–3.5	2.3	1.5–2.7	2.4	1.6–2.6	0.25
AST (U/L)	53	35–88	127	76–199	103	54–155	0.03*
ALT (U/L)	25	20–41	48	35–64	40	30–53	0.02*
GGT (U/L)	119	64–166	169	106–467	208	46–431	0.19
PT (seconds)	15.9	12.4–18.6	16.6	13.5–19.5	12.7	11.4–19.8	0.52
PTT (seconds)	30	27.8–39.0	35	29.9–38.4	32.5	25.8–37.7	0.34
INR	1.7	1.2–1.8	1.7	1.4–1.9	1.4	1.2–2.1	0.74
FEV_1 (%)	101	83–109	54	39–64	63	46–89	<0.01*
FVC (%)	89	80–100	62	22–71	55	43–65	<0.01*
FEV_1/FVC	80	77–84	61	56–68	73	72–79	<0.01*
α_1-AT (mg/dL)	29	27–32	23	21–23	31	21–37	<0.01*

Values are median and 25–75 quartiles (Q82-75). (*) *p*-values of significant difference between normal airflow *vs.* airflow obstruction *vs.* airflow restriction (ANOVA and T-test were applied as appropriate). TB – total billirrubin; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; PT – protrombin time; PTT – partial thromboplastin time; INR – international normalized ratio; FEV_1 – forced expiratory volume at the end of the first second; FVC – forced vital capacity; α_1-AT – alpha$_1$ antitrypsin.

α_1-AT and airflow obstruction, as well as potential interactions with other variables, was assessed through relative risk and multinomial logistic regression analysis. Statistical significant was at p<0.05.

Results

Out of a total of 34 eligible patients, 11 patients showed airflow obstruction, 12 patients showed airflow restriction, and 11 age-matched normal airflow controls participated in the study. Mean age was 52±9.9 years and 91.1% of patients were males. Classic spirometric curves were obtained in each group. Hepatopulmonary syndrome was identified in 67.6% of patients, with 10 in the airflow obstruction group, 8 in the airflow restriction group, and 5 in the normal airflow control group. Clinical and demographic characteristics of the study population are shown in Table 1.

The group with airflow obstruction showed the highest Child-Pugh scores and aminotransferase levels. Other liver function tests were not different among the study groups. Mean serum levels of α_1-AT were 27.3 mg/dL, range 19 to 45 mg/dL. An α1-AT level lower than the median was positively associated

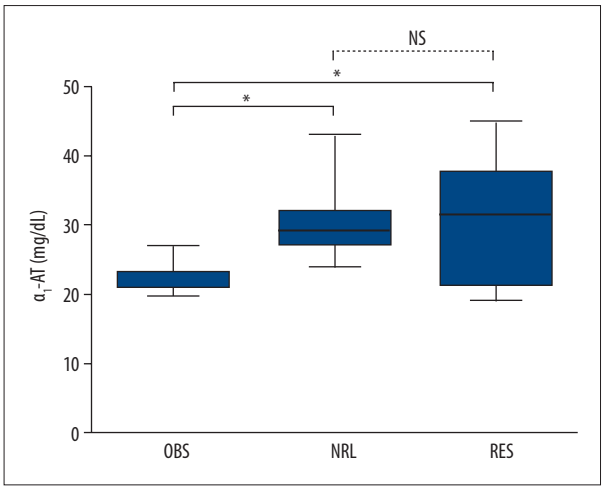

Figure 1. Lower levels of α_1-AT in the group with airflow obstruction. T-test or ANOVA were applied, as appropriate. Statistical difference of α_1-AT values between OBS, NRL, and RES groups (22.5±1.86 mg/dL *vs.* 30.3±5.19 mg/dL *vs.* 30.1±8.93 mg/dL, respectively) is indicated as *(*) p*<0.05. NS – non-significant; α_1-AT – alpha$_1$ antitrypsin; OBS – obstructive airflow; NRL – normal airflow; RES – restrictive airflow.

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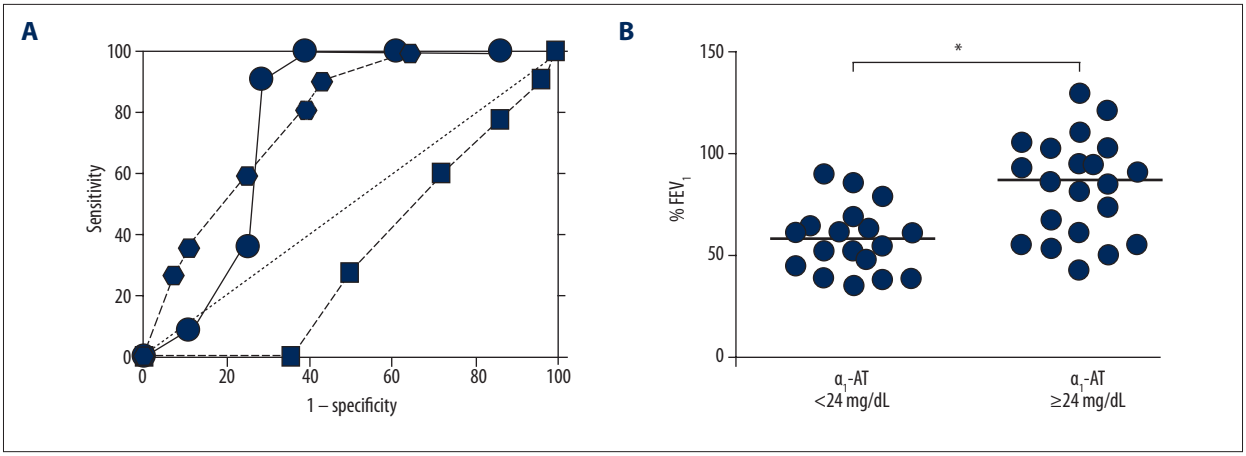

Figure 2. Diagnostic performance of α_1-AT. (**A**) ROC (receiver operating characteristics) analysis to determine α_1-AT cutoff value (24 mg/dL), which best discriminated obstructive airflow. Area under the curve (AUC) for α_1-AT (●—●) compared with AUC for VEF_1 (●—●) and Child-Pugh Score (■—■). AUC=0.687 *vs.* 0.736 *vs.* 0.291 (cutoffs were median values of FEV_1=64% and Child-Pugh score=9). (B) Distribution of FEV_1 (%) according to α_1-AT cutoff value of 24 mg/dL. (*) T-test, p<0.05 difference between α_1-AT<24 mg/dL group *vs.* α_1-AT≥24 mg/dL group. α_1-AT – alpha$_1$ antitrypsin; FEV_1 – forced expiratory volume at the end of the first second; FVC – forced vital capacity.

Table 2. Relation between α_1-AT and spirometric parameters.

Spirometric parameter	r – value	95% CI	*p*
FEV_1	0.46	0.16–0.68	0.003
FEV_1/FVC	0.37	0.009–0.59	0.04
FCV	0.34	0.02–0.60	0.03

Values are mean correlation and 95%CI between serum α_1-AT and spirometric parameters assessing airflow performance. *p*-value refers to the statistical significance of each correlation (Pearson analysis). r – value – mean correlation; 95%CI – 95 percent confidence interval; α_1-AT – alpha$_1$ antitrypsin; FEV_1 – forced expiratory volume at the end of the first second; FVC – forced vital capacity.

with higher Child-Pugh score (cutoff value 9, p=0.0001), higher TB (cutoff 3.6 mg/dL, p=0.0007), and longer clotting times (PT, cutoff value 15 seconds, p=0.005; INR cutoff value 1.52, p=0.005; PTT cutoff value 33 seconds, p=0.003); followed by lower serum albumin (cutoff value 2.3 mg/dL, p=0.03), presence of hepatopulmonary syndrome (p=0.04), and FEV_1 limitation (cutoff value 64%, p=0.04).

The distribution of α_1-AT was significantly decreased in the group with airway obstruction compared with the normal airflow or restrictive airflow groups (Table 1, Figure 1), whereas no difference in α_1-AT was observed between these last 2 groups. Moreover, a moderate positive correlation was found between the α_1-AT serum levels and the values of the different spirometry parameters. A higher correlation with FEV_1 and FEV_1/FVC was observed (Table 2).

To evaluate predictive ability of α_1-AT to discriminate airflow obstruction, ROC (receiver operating characteristics) approach was used (Figure 2A). The cutoff value of α_1-AT best discriminating obstructive airflow was estimated at 24 mg/dL (sensitivity 0.9, specificity 0.72). The area under the curve (AUC) for α_1-AT at this cutoff value was 0.687, not significantly different from the AUC for $FEVP_1$, and both were better than Child-Pugh score, as depicted in Figure 2A (AUC FEV_1=0.736, cutoff at median value of 64% and AUC Child-Pugh=0.291, cutoff at median value of 9, as well as a comparison AUC α_1-AT *vs.* FEV_1, n.s.; AUC α_1-AT *vs.* Child-Pugh Score, p<0.05; AUC FEV_1 *vs.* Child-Pugh score, p<0.05).

Patients with α_1-AT<24 mg/dL registered FEV_1 values significantly lower than those with levels of α_1-AT≥24 mg/dL (FEV_1 of 57.6±16.1 *vs.* 82.3 ±24.4, p<0.001), as depicted in Figure 2B. Likewise, serum α_1-AT level lower than 24 mg/dL was associated to a 10-fold increase in the risk of obstructive airflow (Table 3, upper row). After the stratification analysis for risk adjustment by the clinical-demographic characteristics (Table 3, lower row), being male and older than 52 years old were significant interacting factors. Albumin ≤2.3 mg/dL [RR=8.75 (1.22–62.33, p=0.01)] and PTT <33 seconds [RR=11.25 (1.55–81.17), p=0.01]

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Table 3. Risk of airflow disorders associated to α_1-AT value lower than 24 mg/dL.

	Airflow obstruction		Airflow restriction	
	RR (95%CI)	*p*	RR (95%CI)	*p*
Non-stratified α_1-AT<24 mg/dL	11.6 (1.6–86.5)	0.0007	0.9 (0.5–1.6)	1.0
Stratified by gender				
Male, a1-AT<24 mg/dL	11.17 (1.59–78.45)	0.0007	1.11 (0.49–2.53)	1.0
Female, α_1-AT<24 mg/dL	NA	–	NA	–
Stratified by age				
Older than 52 y/o, α_1-AT<24 mg/dL	8.0 (1.1–53.6)	0.007	0.5 (0.16–1.51)	0.38
Younger than 52 y/o, α_1-AT<24 mg/dL	NA	–	5.8 (0.69–48.8)	0.15

Values are mean relative risk (CI95% range) of obstructive airflow and restrictive airflow associated to a α_1-AT value lower than 24 ng/ml, analyzed as non-stratified risk (upper) and stratified risk by gender and age (lower). *p*-value indicates statistical difference after two tailed, relative risk analysis. RR – relative risk; 95%CI – 95 percent confidence interval; α_1-AT – alpha$_1$ antitrypsin; NA non able to analysis, since limited number of cases in that specific risk group.

showed statistically significant interaction, but less clinical relevancy. This effect seems to be specific for airflow obstruction, since no significant risk or potential interactions were observed for airflow restriction.

Finally, multinomial logistic regression analysis of the basal characteristics revealed that airflow obstruction was associated with lower α_1-AT (Exp[B] 7.25 [1.53–34.25; p=0.012]) and higher Child-Pugh score (Exp[B] 1.45 [1.10–1.90; p=0.008]), after adjusting for age, sex, total bilirubin, albumin, liver enzymes, and clotting test, which indicates their role as strong and independent predictors of airflow obstruction.

Discussion

Severe deficiency of α_1-AT (PiZZ genotype) is a well recognized risk factor for impaired pulmonary function; as well as partial deficiency of α_1-AT (PiMZ heterozygosity) and smoking, which provide significant risk [5]; whereas the risk attributed to α_1-AT gene variants has been less characterized. Nevertheless, the role of α_1-AT, a protein synthesized by the liver, as a marker of airway obstruction in patients with CLD has been poorly explored. The present study included a population of patients with alcohol-related CLD, heterogeneously distributed sex, and who were relatively younger than participants in similar studies [1]; and special care was taken in excluding passive or active smokers, as well as patients with lung damage environmental risk exposure, due to the association with accelerated lung disease, particularly important in a population with intermediate levels of α_1-AT [5,8,9]. The mean serum level of α_1-AT was 27.3 mg/dL in the group of patients without known α_1-AT deficiency. This value falls within the range of α_1-AT determination using an immunoassay method [10].

Lower serum levels of α_1-AT were associated with a more advanced liver dysfunction, and in parallel, the lowest levels of α_1-AT were distributed specifically in the group with airflow obstruction. There was a significant correlation between α_1-AT serum levels and FEV_1, FEV_1/FVC, whereas lower levels of α_1-AT were associated with a 10-fold increase in the risk of an airflow obstructive profile, suggesting the role of α_1-AT as a biomarker of the airflow performance in patients with CLD. Consistently, α_1-AT deficiency or particular genetic variants have been associated with impaired lung function and decline in the clinical prognosis in populations without liver disease [5,11], as well as in patients with CLD [12,13], representing a limitation for liver transplantation [14].

Furthermore, the relationship found between α_1-AT levels and the severity of hepatic dysfunction, both associated with higher lung dysfunction, give rise to some hypotheses regarding performance of α_1-AT system, particularly in CLD, which may accelerate lung damage. Dysregulation of α_1-AT gene expression has been described in hepatic tumors and hepatocarcinogenesis [15]; while the glycosylation patterns of α_1-AT isoforms are modified during progression to cirrhosis and hepatocellular carcinoma [16], which may decrease the proteolytic inhibition activity of α_1-AT [17]. These findings would suggest that the severity of CLD affects the synthesis and glycosylation of α_1-AT, leading to decreased plasma levels and/or functional impairment of α_1-AT, which potentially accelerate lung damage in patients with more advanced CLD.

The relation of α_1-AT has been poorly studied in patients without known α_1-AT deficiency or particular genetic variant. To the best of our knowledge, this is the first study exploring the impact of α_1-AT in the airflow status of patients with CLD. Therefore, the diagnostic ability of α_1-AT was studied in this population using ROC analysis. An α_1-AT cutoff of 24 mg/dL was found to

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provide adequate diagnostic capacity for airflow obstruction (AUC of 0.68, sensitivity of 0.9 and specificity of 0.72), similar to the diagnostic performance of FEV_1 and significantly better than the Child-Pugh score. In addition, the increased risk of airflow obstruction associated with α_1-AT serum levels lower than 24 mg/dL is specific for this spirometric profile, since no risk modification was observed in the population with airflow restriction, whereas sex, age, and Child-Pugh score seem to be factors of potential interaction. Consistently, other studies have found that age and sex (male sex and female in postmenopausal status) are associated with lower FEV_1 and severe COPD in patients with deficiency of α_1-AT (PiZZ genotype) as well as in the general population [18,19], which suggest that sex and age-related changes in pulmonary function are relevant factors to be considered during the study of lung function.

Limitations of our study include potential effects due to the heterogeneity of the population and the sample size. Moreover, the lack of a α_1-AT genotyping and phenotyping for MZ, SZ, and ZZ phenotypes represents a characterization inconvenient as well as a source for further questions. We consider that the screening method combining α_1-AT serum levels and the lack of suggestive history of pulmonary dysfunction reasonably rule out the presence of severe α_1-AT deficiency, although screening for intermediate deficiency, specific profile of α_1-AT genotype, and phenotype are required for better interpretation of the results in the present study. On the other hand, the finding that serum levels of α_1-AT are associated with airflow obstruction in non-primary α_1-AT deficient patients with stable CLD allows identification of patients at risk of lung function impairment, through the determination of a simple, inexpensive serum biomarker, which would allow an estimation of prognosis [20] and would establish early preventive interventions to decrease the negative impact of pulmonary complications in such high-risk patients. In fact, non-primary α_1-AT-deficient patients with CLD may benefit from preventive or therapeutic approaches based on α_1-AT augmentation therapy because the positive impact on clinical prognosis has been demonstrated in similar patients with α_1-AT deficiency [21]. These hypotheses need to be tested in subsequent studies with longitudinal or intervention designs and larger samples.

Conclusions

Serum levels of α_1-AT are related to airflow performance in patients with CLD. Low serum levels of α_1-AT can identify higher risk of airflow obstruction, suggesting its role as a simple, non-invasive biomarker of pulmonary complications in patients with compensated CLD.

Acknowledgments

We acknowldege Microtec Laboratories for technical support and acknowledge financial support from “Programa E015 – Investigación Científica y Tecnológica, ISSSTE”.

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