Serum Aminotransferases and the Severity of Asthma

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The serum enzymes are ideal diagnostic or prediction markers. Aspartate aminotransferase (AST), a mitochondrial and cytoplasmic enzyme, is one of the well-known markers of hepatic, myocardial or skeletal muscle cytolysis, while alanine aminotransferase (ALT) is mainly a hepatic cytoplasmic enzyme. The normal plasmatic values of AST and of ALT reflect a physiological cell turnover. Therefore, both high and low levels of serum liver enzymes might have a clinical significance. We have conducted a retrospective study targeting the association between the serum AST and ALT levels and the lung function impairment among patients with occupational asthma but without hepatic, cardiac, renal or muscular disorders. Our data show a significant relation ($R = 0.54$, $p < 0.05$) between the parameters of obstructive ventilator syndrome and AST and ALT levels, respectively ($R = 0.42$, $p < 0.05$). If this relation is confirmed in prospective studies, serum AST and ALT could become useful markers in monitoring asthma patients.

Keywords: aspartate aminotransferase, alanine aminotransferase, lung function, occupational asthma

Aspartate aminotransferase (AST), also known as glutamate-oxaloacetate transaminase (GOT), catalyzes the reaction between L-aspartate and a-ketoglutarate that leads to oxaloacetate and L-glutamate. This reaction is reversible and takes part in two steps: the first generates oxaloacetate and free pyridoxamine-5'phosphate (PMP) that, consecutively, reacts with a-ketoglutarate to form L-glutamate and to regenerate the pyridoxal-5'-phosphate (P5P), the active form of vitamin B6. Thus, the reaction needs P5P as co-factor in the initial step. AST is known for its role in both maintaining glycolysis by relocation of NADH into mitochondria through the malate–aspartate shuttle pathway [1] and by replenishing the citric cycle and the oxidative phosphorylation. Therefore, together with ALT, AST has an important role in the cell energy production. AST is 20 times of a greater amount than ALT in cardiac and in skeletal muscle; significant amounts are also found in kidney and brain [2]. ALT transforms alanine and α-ketoglutarate in pyruvate and L-glutamate, with multiple consequences in the amino acid and glucose metabolism. The normal levels have been re-evaluated, both for the upper level significance in hepatic diseases [3] and for the lower level for general health indicator and survival [4,5]. An isolated AST elevation is linked to myocardial or musculoskeletal necrosis. Sporadic increases in plasma of AST from the effort of breathing during the asthma attack have been reported [6]. During the evolution of asthma, numerous muscular changes might occur, as a response to the airways resistance and the increase in the respiratory effort [7] or as a side effect of medication, particularly corticosteroids [8]. Reduced physical activity during exacerbations, malnutrition and chronic hypoxia in severe forms, could also contribute to a respiratory and a musculoskeletal atrophy. Decreased plasmatic levels of AST and ALT occur either in severe hepatic failure, or in reduction of muscular mass. In this respect, the aim of the study consisted in exploring a possible relation between serum AST and ALT values and pulmonary ventilator function in asthmatics with occupational exposure.

Experimental part

Clinical and laboratory data of patients diagnosed with occupational asthma, admitted in the Colentina Clinic of Occupational Diseases from October 2017 to December 2017 were assessed. Patients with known hepatic, muscular, renal disease or with acute ischemic heart symptoms during the hospitalization were excluded. A total of 24 patients were included in the analysis. AST and ALT were determined by the standard kinetic method, according to the International Federation for Clinical Chemistry. The normal reference value for AST was 0-42U/L and for ALT 0-48 U/L, respectively. Based on a the AST mean value, the study population was divided in 2 groups: group 1 defined by an AST level below 22 U/L and group 2 with AST values over 22 U/L. De Ritis Ratio (AST/ALT) was also calculated. Lung function was evaluated among patients, within both groups, by spirometry performed with a Jager/Viasys Pneumotachograph, following the standard technique provided by the manufacturer. The reference values and the interpretation of the spirometric testing was done according to the international recommendations [9]. Values of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) are presented as percentage from the reference values. The lung function values determined at patients admission in hospital were considered in the analysis. Data were processed using a StatPlus: Mac Pro. software, version v6, 2016. The Anova analysis was used to assess the differences among variables. Significance threshold was set at 95%.

Results and discussions

All patients were previously diagnosed with occupational asthma or with work related asthma. After applying the exclusion criteria, only 24 patients, predominantly women (n=14) were included in the analysis 11 in group 1, with a mean low values of AST and ALT (16.73, respectively 19.36 U/L), and 13 in group 2 with higher values of AST and ALT (38.23, respectively 39.18 U/L) (table 1). By severity of bronchial asthma, cases were classified into severe (n=6), moderate (n=8) and mild

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Parameter	Study group		Group 1		Group 2	
	Mean	ST Dev	Mean	ST Dev	Mean	ST Dev
Age	54.5	6.2	54.8	6.9	54.4	5.4
BMI	30.4	5.87	28.09	6.86	32.21	4.38
% fVC	82%	17%	81%	22%	82.26%	11.72%
% FEF1	66%	22%	53.09%*	23%	73.94%	15.05%
FEF1/VC	64%	12%	54%*	8.67%	69.82%	9.45%
ASAT	32.43	22.31	16.73*	2.88	38,23	20.19
ALAT	28.43	16.62	19.36*	6.05	39.18	17.18

Table 1
DESCRIPTIVE STATISTICS

Legend: BMI= body mass index; FVC= forced vital capacity; FEV-1= forced expiratory volume in the first second; AST= Aspartate aminotransferase, ALT= Alanine aminotransferase
**p<0.05*

(n=10) forms of disease. The mean value of FEV1 was decreased in group one (53%) versus group 2 (73.94%) (table 1). Mild elevations of AST were noticed in 4 patients, but none of these elevations was 1.5 times higher than the upper reference value. There were 15 patients (62%) with AST/ALT <1. A value higher than 1.5 of the De Ritis ratio was found in 3 asthmatics having both the AST and ALT levels within the normal range values.

Pearson correlation was significant for AST and FEV_1 and FEV_1/FVC. Comparison of the mean abnormal values of the investigated lung function parameters FEV1 and ratio FEV1/FVC between the 2 groups of cases revealed a significant difference ($p < 0.05$) recorded between the reduction of FEV_1 (fig. 1) and ratio FEV_1/FVC (fig. 2) with higher values of AST specific for the group 2.

ALT was also significantly associated with the lung function obstructive indicators ($R = 0.42$, $p < 0.05$ for the FEV_1 association, and $R = 0.54$ $p<0.05$, for the FEV_1/FVC. one).

AST and ALT are the most commonly measured serum enzyme in clinical practice, reflecting mainly the cellular turnover of the liver and of the skeletal muscle cells. Both enzymes are widely distributed in almost all body tissues, but the amount of ALT is very small, except in the liver. In liver, the richer organ in ALT, there is more than three times as much AST than ALT. The reason why plasmatic levels are rather similar is not related to the liver clearance of both enzymes by the sinusoidal cells, with a half-life in the blood circulation higher for ALT (47 h), than for AST (17 hours) [10]. AST has two isoforms: the soluble one which is located in the cytoplasm (and accounts for 20% activity of the liver AST) and the mitochondrial one, with 80% of the liver activity [11]. In liver cytolysis, in which the mitochondrial form predominates, the average plasma half time is even more increased, up to 87 hours [10]; therefore, the AST high level is mainly a marker of necrosis. The significance of the AST elevation was found as a worse prognosis factor of the lung carcinoma and also for other

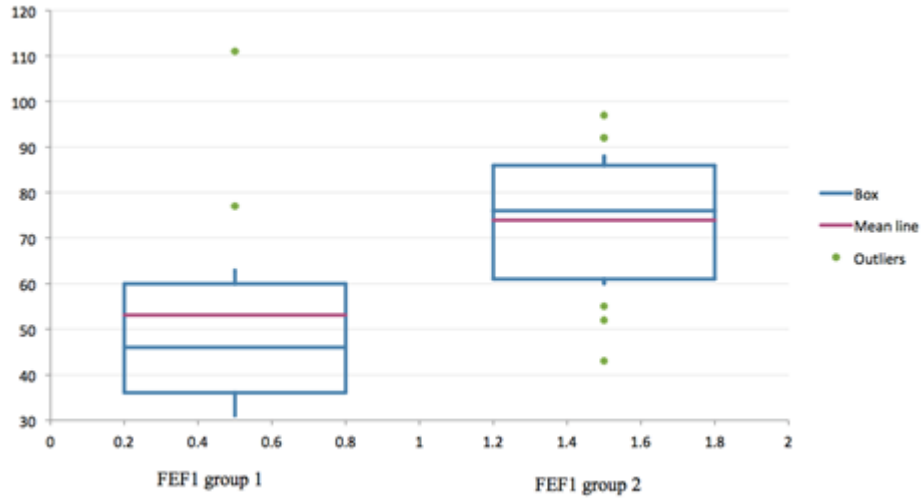

Fig. 1. Comparison of the mean FEV_1 percentage of reduction in the low AST cases (group 1) versus the high AST ones (Group 2)
Legend: FEV-1 = forced expiratory volume in the first second; AST= Aspartate aminotransferase

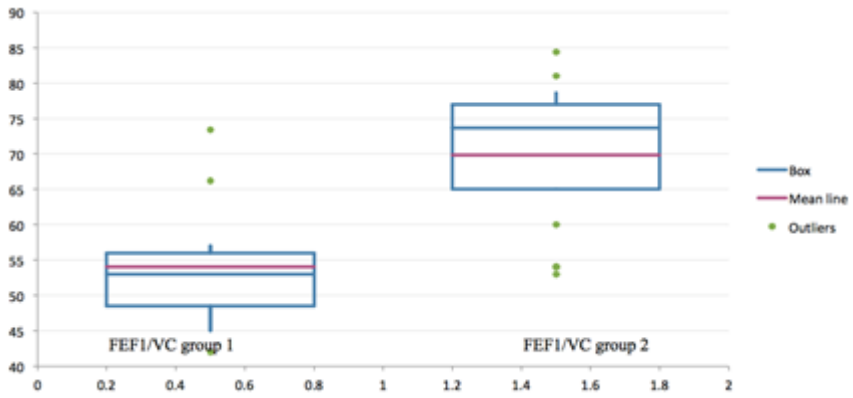

Fig. 2. Comparison of the mean values of the ratio FEV_1/FVC between group 1 (low AST) and group 2 (high AST)
Legend: FEV-1= forced expiratory volume in the first second; FVC= forced vital capacity; AST= Aspartate aminotransferase

forms of cancers [12]. The interest in serum transaminases activity is not limited to the higher values. A low level of serum transaminases activity has been reported in alcoholic liver disease, in other causes of pyridoxal phosphate deficiency or diabetes. However, a high proportion of the low levels are of unknown origin [13]. Our study showed that lower AST and ALT levels are associated with a higher lung function deterioration in asthmatics. Whether this is a specific and causative association, it cannot be proven from a retrospective study and needs a large, prospective one.

Low serum values have been found predictive for the overall mortality [5] in a large cohort study and in another 22.8 years all causes mortality follow up [14]. We are far from a comprehensive understanding of the patho-physiological explanation of the association of high normal value of AST and ALT in patients with occupational asthma and normal lung function. We can only speculate that low levels could reflect the higher degree of sarcopenia and lower energy production; these two, when simultaneously present, could increase the risk for frailty. The anaerobic metabolism during the severe asthma attacks is another possible explanation in line with the interesting observation resulted from an ischemic stroke study, where after the hypoxia correction by supplemental O_2 therapy, expression of AST was induced [15]. Asthmatic patients with more severe bronchial obstruction might have a hypoxemic status that could decrease the enzymes production as producing in liver damage [16]. Although studies referring to other transaminases levels have been published for other obstructive lung diseases [17], to the best of our knowledge, this is the first Romanian research of the relations between AST and ALT and the lung function impairment in patients with occupational asthma. Our study is based on a limited number of patients, because we have excluded possible sources of bias for this association. In this respect, the good statistical correlation factors are relevant for the association.

Conclusions

Serum enzymes are important diagnostic and prognostic markers. The biological significance continues to expand. Low serum levels of AST and ALT are significantly associated with more severe asthma. If this relation is confirmed in prospective studies, serum AST and ALT could become an useful marker of asthma evolution monitoring.

References

1.GREENHOUSE, W.V., LEHNINGER, A.L. Cancer Res **36**, no. 4, 1976, p. 1392.
2.BOTROS, M., SIKARIS, K.A. Clin Biochem Rev **34**, no 3, 2013, p. 117.
3.PRATI, D., TAIOLI, E., ZANELLA, A., DELLA TORRE, E., BUTELLI, S., DEL VECCHIO, E., VIANELLO, L., ZANUSO, F., MOZZI, F., MILANI, S., CONTE, D., COLOMBO, M., SIRCHIA, G., Ann Intern Med **137**, no 1, 2003, p. 1.
4.KIM, W. R., FLAMM, S. L., DI BISCEGLIE, A. M. AND BODENHEIMER, H. C. Hepatology **47**, no 4, 2008, p.1363.
5.RAMATY, E., MAOR, E., PELTZ-SINVANI, N., BROM, A., GRINFELD, A., KIVITY, S., SEGEV, S., SIDI, Y., KESSLER, T., SELA, B.A., SEGAL, G., Eur J Int Med **25**, no 10, 2014, p. 919.
6.TAMARIN F.M., CONETTA R., BRANDSTETTER R.D., CHADOW H., Thorax **43**, no 9, 1998, p.731.
7.LAGHI, F, TOBIN, M.J. Am J Respir Crit Care Med **168**, 2003, p 10.
8.LERU, P., RASCU, A., OTELEA, M., MOHORA, M., MUSCUREL, C., GALCA, M., DINU, V. Rom J Int Med **36**, no 1-2, 1998, p.105.
9.PELLEGRINO, R., VIEGI, G., BRUSASCO, V., CRAPO, R.O., BURGOS, F., CASABURI, R., COATES, A., van der GRINTEN, C.P.M., GUSTAFSSON, P., HANKINSON, J., JENSEN, R., JOHNSON, D.C., MACINTYRE, N. , MCKAY, R., MILLER, M.R., NAVAJAS, D., PEDERSEN, O.F., WANGER, J., Eur Respir J. **26**, nr 5, 2005, p. 948.
10.DUFOUR, D.R., LOTT, J.A., NOLTE, F.S., GRETCH, D.R., KOFF, R.S., SEEFF LB., Clin Chem **46**, no 12, 2000, p. 2027.
11.REJ, R., Clin Lab Med **9**, no 4, 1989, p.667.
12.CHEN, S.L., XUE, N., WU, M.T., CHEN, H., HE, X., Li, J.P., LIU, W.L., DAI, S-Q. Int J Mol Sci **17**, no 9, 2016, p.1474.
13.LUM, G. Lab Med **26**, no 4, 1995, p.273.
14.PELTZ-SINVANI N, KLEMPFNER R, RAMATY E, SELA BA, GOLDENBERG, I, SEGAL, G. J Gen Int Med **31**, no 2, 2016, p.209.
15.KHANNA, S., BRIGGS, Z., RINK, C., Antiox Redox Signal **22**, no 2, 2015, p.175.
16.GROZDAN, A.M., GHIURU, R., BOTEZ C, GAVRILESCU, C.M., DUMA, O., BUZDUGA, O., BUZDUGA, C., GEORGESCU, C., STRAT, L., MUNTEANU, D. Rev Chim. (Bucharest) **67**, no 9, 2016, p.1804.
17.BOZKUS, F., DIKMEN, N., SAHIN, H., SAMUR, A., Respir Care **61**, no 11, 2016, p. 1465.

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