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Alpha-1 antitrypsin, inflammation and quality of life

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Alpha-1 antitrypsin (AAT) is the main circulating serine proteinase inhibitor. A number of studies suggest that AAT can also exhibit biological activity independent of inhibition of serine proteases. The aim of the study was to make experimental investigation of AAT influence on monocytes stimulated by bacterial endotoxyn and to analyze serum AAT concentration in patients with COPD in relation to smoking.

Human blood monocytes were isolated from buffy coats. Serum biomarkers from COPD patients and culture supernatants from donors monocytes were analysed using commercial ELISA kits.

AAT affects monocyte responses to LPS by regulating soluble CD14 release. Here we show that a short-term (up to 2 h) monocyte exposure to AAT leads to an increase of CD14 levels ($p < 0.05$).

In parallel, a short-term (2 h) cell exposure to AAT significantly enhances TNFα release. However, AAT was found to have a dual effect on LPS-induced TNFα release. Thus, during the first 4 h AAT enhanced, while after 8, 12, 18 and 24 h it inhibited LPS-stimulated TNFα release. COPD smokers and ex-smokers showed higher alpha-1 antitrypsin and C-reactive protein serum concentration than never-smokers ($p < 0.05$), that may be important for quality of life and health state. Probably a rapid increase in AAT concentrations during various inflammatory and infectious conditions may enhance the magnitude of monocyte responses to endotoxin and subsequently accelerate resolution of the inflammatory reaction.

Key words: respiratory system, alpha-1 antitrypsin, inflammatory markers, quality of life

INTRODUCTION

Alpha-1 antitrypsin (AAT) is a circulating serine proteinase inhibitor secreted by the liver, which permeates most body tissues where it acts as an inhibitor of a range of proteolytic enzymes (Sitkauskiene et al., 2008). A number of studies suggest that AAT can also exhibit biological activity independent of inhibition of serine proteases (Janciauskiene et al., 2007). Thus, AAT has been reported to play an immunoregulatory role (Li et al., 2009; Janciauskiene et al., 2004) to reduce development of cancer (Serapinas et al., 2010). *In vivo,* AAT has been shown to protect against TNFα or endotoxin-

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induced animal lethality and in a mouse model of lung inflammation AAT was highly effective in suppressing inflammation and connective tissue breakdown (Belge et al., 2002). Immunoregulatory and antimicrobial effect of AAT, resulting monocytes activation is very important for development of chronic inflammatory diseases like chronic obstructive pulmonary disease (COPD).

Peripheral blood monocytes are a population of circulating mononuclear phagocytes that harbor potential to differentiate into macrophages and dendritic cells (Serapinas, Sakalauskas, 2011). These cells of the monocyte lineage are important elements of immune defence because these cells can phagocytize foreign material, present antigen to T cells, and produce a host of cytokines, including TNFα, IL-1 and IL-6 (Mukhopadhyay et al., 2006). Monocytes activation is mainly regulated by expression of membrane CD14 receptors and secretion of soluble serum form (sCD14) (Serapinas, Sakalauskas, 2011). Bacterial lipopolysaccharide binds monocyte surface CD14 receptors and triggers cytokine expression (Brass et al., 2007). It has been suggested that activated peripheral blood monocytes more easily enter the lung and/or stimulate immune activation when present in the lung. Macrophages are the predominant defence cells in the normal lung and are increased during conditions associated with chronic inflammation (Rubins, 2003). A direct role of AAT on monocytes CD14 expression and secretion is unknown.

Therefore, up till now there are no data about exact mechanisms and cellular receptors for new AAT activities. Thus hereditary deficiency of AAT is a well established genetic risk factor for COPD (Senn et al., 2008). However AAT deficiency in COPD patients is an under-diagnosed condition worldwide. The same can be said about Lithuania (Sitkauskiene et al., 2008).

COPD arises as an abnormal inflammatory response of the lung to long-term tobacco smoking or toxic gas inhalation (Garcia-Rio et al., 2010). In patients with COPD lung inflammation is exacerbated by oxidative stress and proteolytic damage by proteinases (Chung, Adcock, 2008). The prevalence of COPD is appreciably higher in men over 40 years of age who are current or former heavy smokers. However, there is consistent evidence that only 15–30% of smokers develop COPD, and that some non-smokers may also develop chronic airflow obstruction, suggesting that the risk for COPD results from a gene-environment interaction (Topic et al., 2011).

Thus there is increasing evidence of systemic inflammation in patients with COPD (Daniels et al., 2010). Smoking may cause a protease-antiprotease imbalance in the lung by reducing the functional activity of AAT in the lung interstitium and 'alveolar' lining fluid, and by increasing the amount of elastolytic proteases released in the lung (Global Initiative for Chronic Obstructive Lung Disease, 2006; Gan et al., 2004). However, the potential role of systemic inflammation in COPD patients with different smoking status has not yet been well established.

MATERIALS AND METHODS

The study consisted of two parts:

I. The investigation of AAT influence on donor monocytes, stimulated by bacterial endotoxyn.

II. The investigation of serum concentration of AAT in COPD patients with different smoking status.

Part I. Monocyte isolation and culture

Human blood monocytes were isolated from buffy coats (in total, blood was obtained from 79 healthy donors) using Ficoll-Paque PLUS (Pharmacia, Sweden). Briefly, buffy coats were diluted 1:2 in PBS with addition of 10 mM EDTA and layered on Ficoll. After centrifugation at 400 g for 35 min at room temperature, the cells in the interface were collected and washed 3 times in PBS-EDTA. Cells were seeded into Petri dishes or 12-well cell culture plates (Nunc, Denmark) at a concentration of 4 × 106 cells/ml in RPMI 1640 medium. After 75 min, non-adherent cells were removed by washing 3 times with PBS supplemented with calcium and magnesium. Fresh medium was added and cells were stimulated with lipopolysaccharide (LPS, 10 ng/ml, Sigma, USA) in the presence or absence of AAT (0.5 mg/ml) at 37 °C, 5% CO_2 for various time points up till 24 h. Cell culture supernatants from monocytes stimulated with AAT or LPS alone or in combination were analyzed to determine soluble CD14 and TNFα levels by using Quantikine ELISA kit (R & D Systems, MN, USA; minimum detection levels less than 125 and 15.6 pg/ml). In some experiments monocytes were

stimulated with LPS, AAT or their combination in the presence of 4 μg/ml monoclonal anti-human CD14 antibody (R & D Systems, MN, USA).

Part II. Analysis of COPD patients

Patients with COPD were recruited for the study from different Lithuanian regions (namely: Kaunas, Vilnius, Šiauliai, Klaipėda and Alytus). A total of 355 COPD patients, diagnosed according to the criteria of The Global Initiative for Chronic Obstructive Lung Disease (GOLD), who gave their informed consent, underwent further examination. Smoking history was calculated in pack-years as the product of tobacco use (in years) and the average number of cigarettes smoked per day/20 (years × cig. per day/20).

Blood samples were drawn in serum tubes, clotted at room temperature for 30–60 min and centrifuged for 15 min at 4 000 rpm. Then, serum samples were immediately frozen at –70 °C for further assay.

Serum concentrations of AAT were determined by means of nephelometry using commercially available kits (Dade Behring Marburg GmbH, Germany) according to the manufacturer's instructions.

Statistical analyses

Statistical analysis was performed with the SPSS 15.0 program (serial code 9880215). Quantitative variables were expressed as means with standard deviations (SD) or median and quartiles. Some values were compared using the Student's t-test and one-way ANOVA. Differences of quantitative data that had not improved the normal distribution were assessed by Mann-Whitney *U* test and Kruskal-Wallis *H* test. Correlation between continuous parameters was determined by Spearman's rank correlation coefficient (*r*). A *p* value of less than 0.05 was considered significant.

RESULTS

AAT effect on monocytes stimulated by bacterial endotoxyn. The first task was to determine whether AAT alone or in combination with LPS has any effect on soluble monocytes differentiation factor CD14 (sCD14) levels. As shown in Fig. 1, AAT induced a fast sCD14 release from monocytes compared to non-treated controls. Nearly identical induction of sCD14 release was detected in cells exposed to AAT/LPS combination, whereas LPS alone had no significant effect on sCD14 levels (Fig. 1).

The finding that AAT affects sCD14 level prompted us to investigate whether AAT also affects monocyte responses to LPS in a time-dependent manner. Thus, LPS (10 ng/ml) was added to human monocytes with or without AAT (0.5 mg/ml) for 30 min, 1, 2, 4, 6, 8, 12, 18 and 24 h, and cell supernatants were analyzed for TNFα release. Cells stimulated with AAT alone

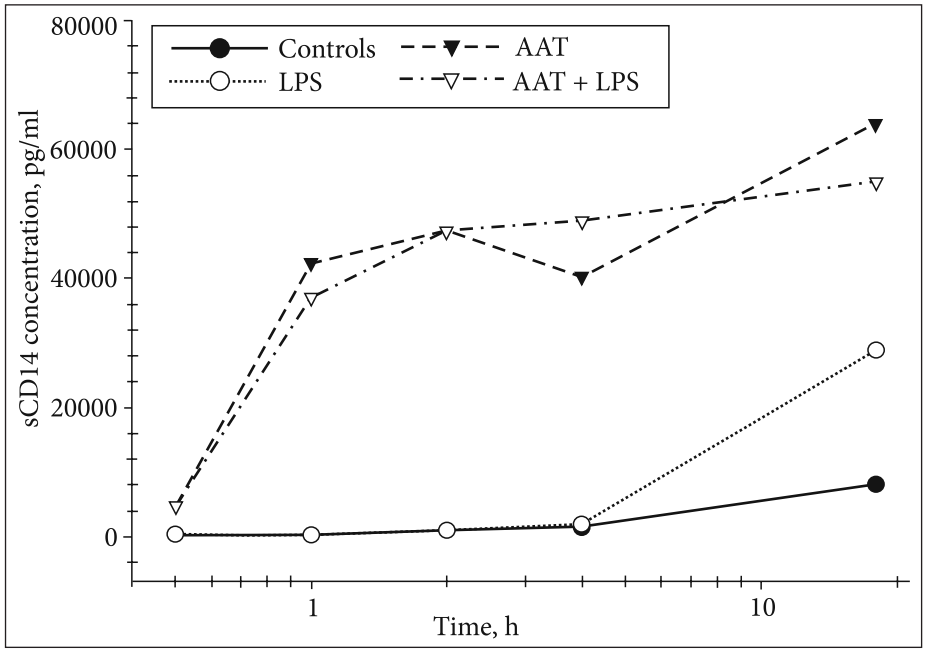

Fig. 1. Effects of AAT on sCD14 secretion

Monocytes were treated with a fixed concentration of AAT (0.5 mg/ml), LPS (10 ng/ml) or their combination for various time points. Cell supernatants were collected; sCD14 levels were measured by ELISA. Bars represent mean of two experiments with duplicates for each experiment

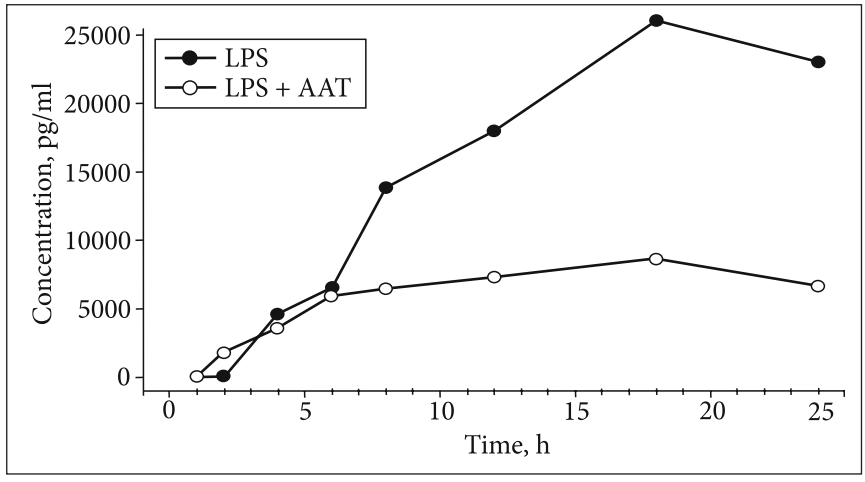

Fig. 2. Effects of AAT on LPS-induced TNFα release from human monocytes

LPS (10 ng/ml) was added to adherent-isolated monocytes isolated with and without AAT (0.5 mg/ml) for 30 min, 1, 2, 4, 6, 8, 12, 18 and 24 h. Cell supernatants were collected, TNFα levels were measured by ELISA

served as a negative control. As shown in Fig. 2 LPS triggers a release of TNFα by monocytes in a time-dependent manner. However, AAT was found to have a dual effect on LPS-induced TNFα release. Thus, during the first 4 h AAT enhanced, while after 8, 12, 18 and 24 h it inhibited LPS-stimulated TNFα release. The most potent enhancement of LPS-stimulated TNFα release by AAT was observed at 2 h (Fig. 2).

In order to investigate whether sCD14 is involved in the effects of AAT on LPS-induced cytokine release, we neutralized the sCD14 protein with 4 μg/ml of neutralizing monoclonal antibody. Anti-sCD14 antibody reduced LPS-stimulated TNFα release by 38%, $p < 0.01$. AAT/LPS-stimulated TNFα release was also significantly inhibited in the presence of antibody (75%, $p < 0.001$) after 2 h compared to cells treated with LPS/AAT (Fig. 3).

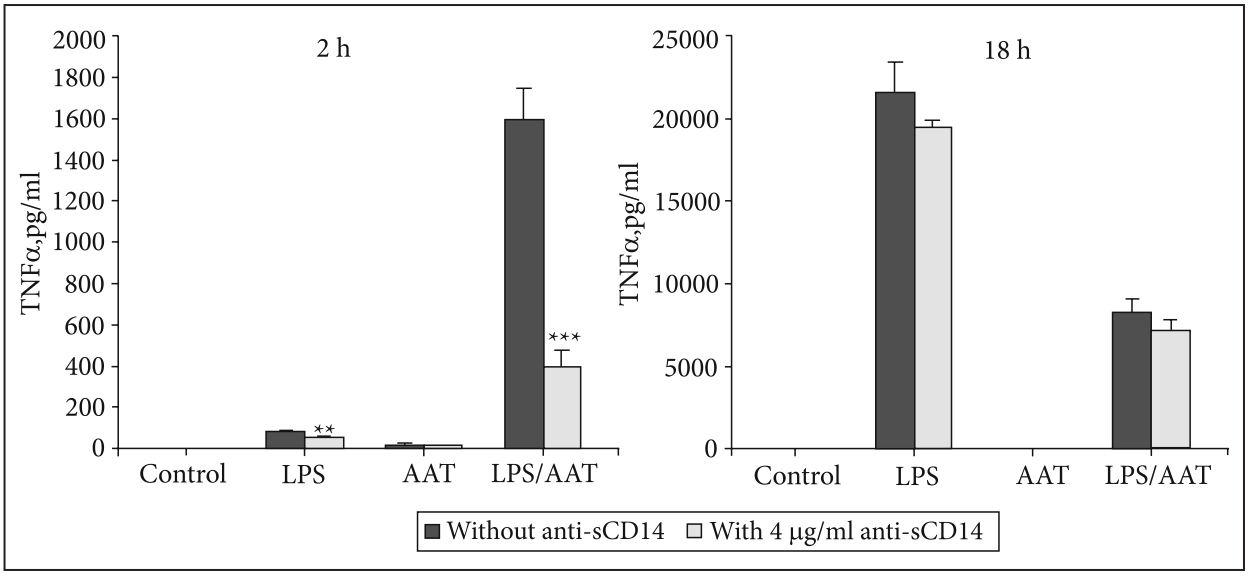

Fig. 3. Effects of anti-human sCD14 antibody on LPS and LPS/AAT induced TNFα release by monocytes

Monocytes were stimulated with LPS (10 ng/ml), AAT (0.5 mg/ml) or LPS/AAT combination alone or in the presence of 4 μg/ml of azide-free anti-sCD14 antibody for 2 and 18 h. TNFα was measured in cell culture supernatants harvested after 2 and 18 h incubation. Bars represent the mean ±SEM (**$p < 0.01$; ***$p < 0.001$)

However, monocytes stimulated with LPS or AAT/LPS combination in the presence of anti-sCD14 for 18 h showed no significant changes.

Serum concentration of AAT in COPD smokers, ex-smokers and never-smokers. Higher prevalence of COPD is found in smokers and in general smoking is the most important factor in COPD pathogenesis, so we analysed possible associations between smoking status and inflammatory biomarkers. Results of smoking status influence on AAT level revealed differences in AAT concentration. Fig. 4 shows that AAT concentration in smokers (1.75 ± 0.51) and ex-smokers (1.69 ± 0.43) was higher than in never-smokers (1.49 ± 0.38) ($p < 0.05$).

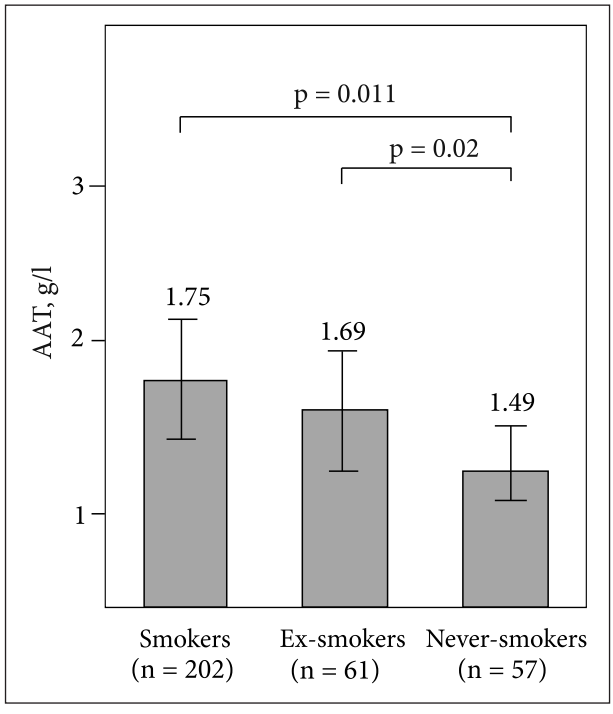

Fig. 4. Serum AAT concentration in COPD smokers, ex-smokers, never-smokers without AAT deficiency

Data are presented as mean ± SD

DISCUSSION

AAT, one of the major serine proteinase inhibitors, is classified as an acute phase protein and increases in concentration during various inflammatory responses. We analyzed short-term (2 h) and long-tem (18 h) monocyte responses to LPS and AAT separately or in combination. Our results clearly show that within 2 h AAT alone as well as with LPS, strongly up-regulates sCD14 secretion. We also measured sCD14 concentrations in cell culture supernatants even after 18 h, and found that the concentration of sCD14 was much higher in monocytes treated with AAT and AAT/LPS combination compared to controls or LPS-treated cells. This latter observation provides evidence that a direct relationship exists between the accumulation of sCD14 and acute inflammatory phase duration. The biological function of sCD14 is so far not clear. *In vitro*, an excess of sCD14 is shown to inhibit LPS binding to mCD14 and hence block cellular activation (Hojman et al., 1997). Data show that binding of LPS to monocytes and LPS-induced cell activation are abrogated by an exogenously added high dose of sCD14 (Serebrina et al., 2008). sCD14 itself appears to interact with LPS and play a role in the neutralization of LPS (Pugin et al., 1993). On the other hand, low amounts of sCD14 are suggested to play a role in sensitizing normal human phagocytes to low endotoxin concentrations (Hojman et al., 1997). Our findings reveal that after 2 h incubation with AAT the monocyte supernatant levels of sCD14 are about 16 ng/ml, which is similar to previously described optimal levels needed for enhancement of LPS-induced cell activation. Accordingly, our data show that monocyte exposure to LPS for 2 h led to an activation of NF-κB (p50/p65) in concert with a large release of pro-inflammatory cytokine. Indeed, simultaneous treatment of monocytes with LPS and AAT amplified LPS-induced pro-inflammatory cytokine TNFα release. However, sCD14 levels in AAT-stimulated monocytes increased to about 30 ng/ml after 18 h, which suggests that the long-term effects of AAT on LPS-induced monocyte activation might be related to the highly elevated sCD14 levels that lead to reduction in monocyte responsiveness to LPS. As predicted, a long-term (18 h) exposure of monocytes to LPS, AAT or their combination shows that AAT significantly inhibits LPS induced pro-inflammatory cytokine TNFα secretion. Here we show that neutralization of sCD14 with anti-CD14 antibody significantly reduced AAT capacity to enhance monocyte response to LPS in the short-term (2 h), whereas it had no effect in the long-term (18 h). The data support the hypothesis that a modulation of LPS-induced monocyte

activation by AAT may be related to the AAT-induced modulation of CD14 levels. This may be a physiologically important mechanism by which AAT damps inflammatory processes. A rapid increase in AAT concentrations during various inflammatory and infectious conditions may enhance the magnitude of monocyte responses to endotoxin and subsequently accelerate resolution of the inflammatory reaction.

In clinical part of the study the findings show that current smokers and ex-smokers had higher circulating AAT levels compared to non-smokers. These results suggest that smoking may be associated with higher AAT secretion in the liver of COPD patients and mechanisms connected with systemic inflammation which continues even after cessation of smoking. Even in healthy individuals, positive associations between active smoking and AAT levels have been reported before (Senn et al., 2008). The quantity of AAT that diffuses passively from the blood to the lung increases during an inflammatory process, which takes place in COPD (Global Initiative for Chronic Obstructive Lung Disease, 2006). This may indicate increased requirement of AAT to meet the needs of overcoming the release of various enzymes from neutrophilic cells in the lungs, but its protective function may be overrun by the high concentration of proteases (Tanni et al., 2010). The increase of AAT level in smokers and ex-smokers reflects the dual role of AAT as a respiratory disease biomarker. The net impact of AAT on lung function seems to be a result of context-dependent (i. e. AAT genotype) and contrasting protective and inflammatory effects in respiratory tract. On the one hand, elevated serum AAT can reflect a beneficial shift in the protease-antiprotease balance, the centre piece of the pathophysiological pathway mediating the effect of severe congenital AAT deficiency on COPD. On the other hand, elevated serum AAT can also reflect low-grade inflammatory processes in the lung, it is hypothesized COPD risk factor (Karadag et al., 2008).

There is consensus about the presence of small airway and lung parenchyma inflammation in smokers and COPD patients (Abboud, Vimalanathan, 2008; Serapinas et al., 2011). Local inflammation is characterized by increased numbers of inflammatory cells, such as neutrophils, lymphocytes, and macrophages and higher TNF-α and IL-8 concentrations in smokers, than healthy controls (Croft, 2009; Horiuchi et al., 2010; Bradley, 2008). However, even after cessation of smoking the inflammatory state changes only in asymptomic ex-smokers, but not in COPD ex-smokers (Gamble et al., 2007; Willemse et al., 2005). Gamble et al. compared bronchial biopsies of COPD current smokers and COPD ex-smokers and did not find any differences in cell counts or inflammatory markers (especially TNF-α) between groups (Gamble et al., 2007; Battaglia et al., 2007). We did not analyze local inflammation in our study and some data suggest that local and systemic inflammation can be regulated differently (Willemse et al., 2005). Thus inflammatory marker associations are complex and better understanding of various mediators interplay will require appropriately designed further studies.

In conclusion, smoking status has various impacts on systemic inflammation and higher inflammatory marker levels in current smokers and ex-smokers show that in COPD inflamation continues for many years after smoking cessation. These data support the concept that pulmonary obstruction may be a consequence of the presence of smoking induced inflammatory stimuli.

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ALFA-1 ANTITRIPSINAS, UŽDEGIMAS IR GYVENIMO KOKYBĖ

Santrauka

Alfa-1 antitripsinas yra pagrindinis cirkuliuojantis serino proteazių inhibitorius. Naujausi tyrimai rodo, kad alfa-1 antitripsinas pasižymi ir kitomis savybėmis, nesusijusiomis su antiproteazine funkcija. Tyrimo tikslas – ištirti alfa-1 antitripsino poveikį stimuliuotų monocitų aktyvumui *in vitro* bei išanalizuoti sergančiųjų lėtine obstrukcine plaučių liga alfa-1 antitripsino koncentracijos pokyčius rūkymo metu. Tyrėme alfa-1 antitripsino poveikį bakteriniu endotoksinu stimuliuotiems monocitams, išskirtiems iš donorų kraujo. Biožymenų koncentracija serumo mėginiuose nustatyta imunofermentiniu ELISA metodu. Tyrimo duomenimis, trumpalaikė (po 2 val.) monocitų stimuliacija alfa-1 antitripsinu skatina jų tirpaus CD14 žymens sekreciją ir padeda monocitams greičiau atpažinti ir neutralizuoti bakterinį endotoksiną. Trumpalaikė (po 2 val.) monocitų stimuliacija alfa-1 antitripsinu skatina, o ilgalaikė (po 18 val.) – slopina bakterinio endotoksino sukeltą TNFα sekreciją, o tai rodo uždegimą moduliuojantį alfa-1 antitripsino poveikį apsaugant monocitus nuo hiperstimuliacijos bakteriniu endotoksinu. Rūkančių ir metusių rūkyti sergančiųjų lėtine obstrukcine plaučių liga alfa-1 antitripsino koncentracija kraujo serume buvo didesnė nei nerūkančiųjų ($p < 0,05$), ir tai patvirtina alfa-1 antitripsino svarbą gyvenimo kokybei bei lėtinių plaučių ligų dėl rūkymo atsiradimui.

Raktažodžiai: kvėpavimo sistema, alfa-1 antitripsinas, uždegimo žymenys, gyvenimo kokybė