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Original research article

Assessment of serum levels of DIO1 and DIO3 in patients diagnosed with COPD

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease is the most common chronic lung disease, which may be caused by different pathological processes, including inflammation. Furthermore, signs of changes in thyroid hormone levels are found in some patients. Deiodinases (DIOs) are selenoproteins (enzymes) involved in the synthesis of thyroid hormones. It has been found that these molecules are involved in inflammatory processes. We carried out this preliminary study to investigate the levels of two deiodinases, i.e. type 1 deiodinase (DIO1) and type 3 deiodinase (DIO3), and their possible association with COPD and specific clinical parameters.

Patients and methods: Serum levels of DIO1 and DIO3 as well as lung function parameters were measured in 50 patients suffering from COPD and 30 healthy control subjects. The Mann-Whitney *U* test and Pearson's correlation coefficient were used to compare and correlate data.

Results: Serum levels of DIO1 and DIO3 were significantly elevated in COPD patients (97.9 ± 55.6 versus 28.2 ± 28.3 U/L for DIO1 and 19.6 ± 10.7 versus 6.4 ± 6.3 U/L for DIO3; $p < 0.001$). No correlation between serum levels of the examined DIOs and other sociodemographic and clinical parameters was identified in this study.

Conclusion: For the first time we observed that peripheral DIO1 and DIO3 concentrations were elevated in COPD; hence, we may cautiously begin considering these molecules as potential circulating biomarkers of COPD. It may also be beneficial to conduct further studies to confirm and clarify their potential role.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the leading risk factor for morbidity and mortality. The prevalence of this disease among general population is approximated at 10% worldwide. According to recent data, COPD is considered the fourth most important cause of death [1,2]. The disease is known as one of the illnesses the etiology and pathogenesis of which are multifactorial. Not completely reversible and progressive airway obstruction is a predominant and characteristic feature of COPD [3]. Different levels of inflammation represent an important process involved in the etiology of COPD. This process is observed on the surface of lungs, while signs of chronic and systemic inflammation are also noticeable [4,5]. The involvement of many inflammatory and immune-associated molecules and cells is also indicated and discussed in the literature [4].

The widely discussed and investigated inflammatory molecules include tumor necrosis factor-alpha (TNF-alpha). Certain results indicate that higher serum levels of TNF-alpha are observed in patients with stable COPD and in patients with exacerbation as compared to controls [6]. IL-6 is yet another inflammatory molecule the level of which is confirmed to be changed during COPD. Moreover, the widely examined COPD biomarkers include IL-1, IL-8, and Creactive protein (CRP), which are all higher in patients affected by COPD when compared to healthy subjects [7]. The role of systemic inflammatory markers in the pathogenesis of COPD was reviewed and confirmed in a meta-analysis [8].

Several recent studies have revamped the interest and demonstrated that „generally not linked" molecules play the role of immuno-inflammatory components. Such molecules include type 1,2,3 iodothyronine deiodinase (DIO1,2,3), i.e. an enzyme participating in the synthesis of the thyroid hormone (TH) [9], the important targets of which are immune cells [10]. Two dissimilarly acting deiodinases that affect TH levels are represented by DIO1 and DIO3.

The majority of circulating T3 is produced by DIO1. The enzyme involved in reductive deiodination is DIO3; it eliminates T4 by means of its transformation to reverse T3 (rT3) and diiodothyronine (T2). DIO1 expression is observed in the thyroid gland and kidneys. DIO1 is also expressed in lymphocytes; it has been confirmed that DIO1 levels are

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influenced by pro-inflammatory cytokines [9], the signal messengers that play a role in the complex network within the immune system to coordinate the inflammatory response. Several studies have demonstrated a correlation between respective cytokines and deiodinase expression levels. For example, IL-1, IL-6, and TNF-α affect T3 mediated induction of mRNA for DIO1 [11,12]. Similarly, IFN-ɣ reduces DIO1 enzyme activity [13].

Under normal conditions, DIO3 can be found in the majority of organs, including the brain [9]. Recently, the presence and subcellular location of DIO3 on transcriptional levels has been confirmed in human neutrophils [10]. Aberrant expression of DIO3 is observed in the case of pathological conditions [14]. For example, high expression of DIO3 is demonstrated in activated monocytes, macrophages, and granulocytes, which supports the hypothesis that DIO3 plays a role in chemical and bacterial inflammation [15,16]. Bacterial outgrowth in blood, spleen, and lungs of D3KO mice is significantly higher. In addition, the protective role of DIO3 against inflammation is suggested [17]. To shortly sum up, deiodinases – including DIO1 and DIO3 – interfere with immuno-inflammatory processes, and influence the expression and release of inflammatory cytokines [18].

The levels and the role of DIO1 and DIO3 in COPD have not been examined yet; no evidence makes it possible to determine whether this disease is associated with changes in DIO1 and DIO3 levels. Therefore, taking into consideration that DIO1 and DIO 3 may interact with immune cells and inflammatory biomarkers, and are also considered to be possible targets in immuno-inflammatory processes characteristically observed in COPD, we aimed to investigate the levels of these molecules in COPD.

2. Patients and method

2.1. Patients selection

Fifty patients, diagnosed with third stage COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), were selected to participate in this study. In all of the studied patients, two exacerbations of moderate intensity or one that required admission to a hospital's pulmonology ward were noted. These patients were initially treated at the Department of Pneumology and Allergy, and later in an outpatient clinic. All the patients were ex-smokers. In the study group, smoking history totaled between 25 and 40 years, and the average number of cigarette pack-years was 25. The group of control subjects comprised 30 individuals – gender- and age-matched, selected among healthy community individuals invited to take part in the study based on the absence of diagnostic criteria.

2.2. Diagnostic procedure

All the patients were subjected to detailed diagnostic procedure, which included clinical examination, spirometry, gasometry, and anthropometry. The pulmonary function was tested in clinically stable patients using the LUNGTEST 1000 spirometer in a sitting position after minimum 15-min rest. The patients were instructed to avoid short-acting β_2-agonists at least 6 h before testing and long-acting β_2-agonists at least 12 h prior to the lung function test. Gasometry was measured using arterial blood according to the required standards, and the test was performed using the Corning 348 Blood Gas Analyzer (Ciba Corning, USA).

Body weight and height were measured in all the patients to calculate the body mass index (BMI), while waist and hip circumference enabled the calculation of the waist-to-hip ratio (WHR).

Exacerbations in the course of the study were excluded based on laboratory tests (blood cell count with smear, CRP) and clinical presentation (absence of dyspnea, normal body temperature, no green sputum expectoration). Lung tumors were excluded using radiological modalities (X-ray, computed tomography).

2.3. Deiodinase measurements

Venous blood samples were drawn and collected into sterile tubes (2 × 5 ml) without anticoagulants and stored at room temperature for about 30 min to enable clot formation; then the samples were centrifuged for 15 min at approximately 1000 × *g*. After the centrifugation, the serum was removed and stored aliquot at −80 °C.

DIO1 and DIO3 were measured using commercially available Human DIO1 ELISA Kit (MyBiosourse, San Diego, CA, USA) and Human DIO3 ELISA Kit (MyBiosourse, San Diego, CA, USA). All calculations were performed according to the instructions and protocols provided by the manufacturers. The absorbance of the samples was measured using Multiskan Ascent Microplate Photometer BioTek El 808 (BioTek, Winooski, Vermont, USA) at λ = 450 nm. Analytical curves for the analyzed proteins were worked out to determine protein concentration. Serum DIO1 and DIO3 protein was presented as U/L.

2.4. Statistical analysis

All data analyses were performed using Statistica (version 12.0). A statistical analysis of the collected material included calculation of both descriptive and inferential statistics. The results are presented as percentages (%) or means (M) with standard deviations (± SD). The chi-square test and Mann-Whitney *U* test were used to compare demographic variables (gender and age) between the patients and controls. The comparison of DIO1 and DIO3 concentration between the subjects with COPD and the controls was performed using the non-parametric Mann-Whitney *U* test. To evaluate the relationships between the analyzed protein levels and other variables, we calculated Pearson's correlation. To account for the effect of sex, BMI, WHR, on the relationship between COPD status and DIO level, a logistic regression model was used. Statistical significance was defined as $p < 0.05$ for all the analyses.

2.5. Ethical issues

The studies were conducted according to the principles of 1964 Helsinki Declaration with its later amendments.

All procedures were reviewed and approved by the Local Bioethics Committee of Medical University of Lodz, Poland (No. RNN/4/12/KE).

3. Results

A total of 80 subjects, including patients and healthy controls, were enrolled to this experiment. Baseline characteristics of the subjects are summarized and presented in Table 1. Anthropometric and spirometric data can be found in Tables 2 and 3. There were no differences with respect to age ($z = 1.61$, $p = 0.1$), gender ($\chi 2 = 1.79$, $p = 0.1808$), and BMI ($z = 0.79$, $p = 0.43$). However, differences in terms of WHR ($z = 3.81$, $p = 0.000137$) between the COPD patients and the controls were observed. As expected, a significant reduction in FEV1, FV1/CV, and FVC in the COPD patients was confirmed after a comparison with the controls ($z = -7.45$, $p < 0.001$; $z = -7.06$, $p < 0.0001$; $z = -7.19$, $p = < 0.0001$, respectively).

The recorded results indicated that serum levels of DIO1 and DIO3 were significantly elevated in the patients diagnosed with COPD when compared to the control group. Detailed results can be found in Table 4.

There were no statistically significant differences observed in the serum protein concentrations of DIO1 and DIO3 between males with COPD and healthy males, and also between women with COPD and healthy female subjects (Mann-Whitney *U* test, $p < 0.05$, for DIO1 $p = 0.81$, for DIO3 $p = 0.68$).

The correlation between DIO1, DIO3 and other parameters is presented in Table 5.

We observed a positive relationship between serum levels of DIO1 and DIO3 in the patients with COPD ($r = 0.977163$, $p < 0.05$) and in

Table 1
Patients baseline characteristic.

Variable	Patients with COPD	Controls	Statistical analysis
Number of subjects	50	30	
Sex F(%):M	19(38):31	16(53.33):14	p = 0.1808 $\chi 2$ = 1.79
Ethnic origin (%)	Caucasian (100%)	Caucasian (100%)	
Age (years)			
M ± SD	65.70 ± 8.20	62.70 ± 7	p = 0.1
Median	65.50	63.00	z = 1.61
Age women (years)			
M ± SD	66.16 ± 8.00	62.25 ± 7.10	p = 0.16
Median	67.00	62.00	z = – 1.41
Age men (years)			
M ± SD	65.48 ± 8.45	63.21 ± 7.14	p = 0.37
Median	65.00	63.50	z = – 0.89

Values are presented as mean (M) with the standard deviation (SD). COPD – chronic obstructive pulmonary disease; p – level of statistical significance; z – Mann-Whitney *U* test.

Table 2
Anthropometric parameters of study group.

Variable	Patients with COPD	Controls	Statistical analysis
BMI (kg/m^2)			
M ± SD	27.6 ± 11.3	25 ± 4.6	p = 0.43
Median	25.7	25.8	z = 0.79
WHR			
M ± SD	1.0 ± 0.1	0.8 ± 0.1	p = 0.000137
Median	1.0	0.9	z = 3.81

COPD – chronic obstructive pulmonary disease; BMI – body mass index; WHR – waist-to-hip ratio; M – mean; SD – standard deviation; p – level of statistical significance; z – Mann-Whitney *U* test.

Table 3
Spirometric characteristic of the study patients.

Variable	Patients with COPD	Controls	Statistical analysis
FEV1			
M ± SD	40.1 ± 14	102.8 ± 6	p < 0.001
Median	38.5	102.0	z = -7.45108
FEV1/VC			
M ± SD	65.5 ± 16.6	100.4 ± 11.6	p < 0.0001
Median	60.5	97.5	z = -7.05856
FVC			
M ± SD	65.8 ± 13.3	109.4 ± 11.1	p = 0.0001
Median	64.5	109.0	z = -7.05856

COPD – chronic obstructive pulmonary disease; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity; M – mean; SD – standard deviation; p – level of statistical significance; z – Mann-Whitney *U* test.

the healthy subjects (r = 0.919270, p < 0.05). The analysis of association calculated with the use of a logistic regression model showed no correlation between DIO1, DIO3 and COPD severity, however, we noted a correlation between DIO1 and BMI in the patient population as a whole (b = 0.32).

4. Discussion

This main aim of the study was to evaluate the serum levels of DIO1 and DIO3 in the patients diagnosed with COPD. The main and most important finding is that the concentration of the two investigated molecules is highly elevated in the COPD patients as compared to healthy controls. To our best knowledge, this experiment was the first to examine and investigate the protein levels of DIO1 and DIO3 in COPD. In general, based on the available scientific knowledge, the levels of both enzymes are investigated rather rarely. The expression levels of DIO1 in human polymorphic mononuclear cells were examined in patients suffering from Graves' disease [19]. Blood expression of mRNA for DIO1 and DIO3 and serum protein levels has been recently examined by our team on a group of patients diagnosed with recurrent depressive disorders [20].

Changes in the levels of DIO1 and DIO3 during COPD may have a multidirectional background. The two proteins (enzymes) are involved in the synthesis of THs [9]. Our data may open a discussion regarding the involvement of DIO1 and DIO3 in the determination of THs levels and their possible influence on the course of the disease. Disturbances related to low and high levels of THs are found in COPD. The observed changes include hypo- and hyperthyroidism [21,22]. THs levels correlate with the clinical features characteristically observed in COPD. For example, a relationship was found between TH levels and blood gas parameters, including lower blood oxygen pressure and higher blood carbon dioxide pressure, in patients with hypothyroidism [23]. Furthermore, a correlation was indicated between low conversion from T4 to T3 and hypoxemia in severe cases of COPD [24]. Similarly, hyperthyroidism affecting the breathing pattern in patients suffering from COPD, dyspnea, hyperventilation, and muscle weakness are also

Table 4
Statistical analysis describing differences in protein levels between patients with COPD and controls.

Variable	Patients with COPD	Controls	Statistical analysis
DIO1 U/L			
M ± SD	97.9 ± 55.6	28.2 ± 28.3	p < 0.001
Median	98.6	20.5	z = 5.64980
DIO3 U/L			
M ± SD	19.6 ± 10.7	6.4 ± 6.3	p < 0.001
Median	19.2	4.7	z = 5.5173

COPD – chronic obstructive pulmonary disease; M – mean; SD – standard deviation; p – level of statistical significance; z – Mann-Whitney *U* test.

Table 5
Correlation between DIO1 protein levels and other parameters.

	Patients with COPD		Controls	
	n = 50		n = 30	
	r	p	r	p
DIO1 and age	−0.07		0.21	
DIO3 and age	−0.09		0.14	
DIO1 and BMI	**0.32**	**< 0.05**	0.17	
DIO3 and BMI	**0.29**	**< 0.05**	0.19	
DIO1 and WHR	0.09		**0.47**	**< 0.05**
DIO3 and WHR	0.09		**0.44**	**< 0.05**
DIO1 and FEV1	−0.07		−0.15	
DIO3 and FEV1	−0.10		−0.15	
DIO1 and FEV1/VC	0.19		−0.09	
DIO3 and FEV1/VC	0.15		0.10	
DIO1 and FVC	−0.14		0.03	
DIO3 and FVC	−0.15		−0.16	

COPD – chronic obstructive pulmonary disease; n – number of subjects; r – correlation coefficient; p – level of statistical significance; BMI – body mass index; WHR – waist-to-hip ratio; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity.
Statistically significant values are provided in bold font.

observed [23,25].

The obtained results suggest that DIO1 levels are increased in COPD patients. Such findings may partially explain why some patients with the disease in question are characterized by high levels of THs, especially T3 [26]. Increased DIO1 may result in intensive deiodination of T4 in overt hyperthyroidism – a state observed in a specific group of patients with COPD [27]. A link between the concentration of respective DIOs and TH levels cannot be excluded. Nevertheless, other factors determining T3 levels should be taken into account. For example, cigarette smoking is positively correlated with total T3 levels [28]. The team of researchers examined DIO1 in lung cancer tissue and compared it with peripheral tumor tissue. Based on the results recorded, higher DIO1 activity was observed in the peripheral tissue as opposed to the cancer tissue. Nevertheless, no significant tendency for the correlation of DIO1 activity and the grade of differentiation (G1-G3) of the tumor tissue and the stage of lung cancer was observed [29]. Our results are not in line with the data which indicate that during inflammation, IL-1, IL-6, and other cytokines, reduce the expression levels of DIO1, including its mRNA and activity [13,30] via a different mechanism, for example the NADPH oxidase pathway [31].

During our experiment we also revealed increased levels of DIO3 in COPD as compared to the group of control subjects. These results seem to be a part of the discussion explaining low THs levels in COPD. The levels of the two opposing enzymes are elevated and both enzymes may participate in COPD independently, affecting different processes.

One of the typical features of COPD is the presence of inflammation; hence, investigating inflammatory biomarkers in COPD is required [4]. The two types of deiodinases examined are involved in the inflammatory process. Under the influence of inflammatory factors, DIO1 decreases. The mechanism involved includes competition of cytokine for activator protein-1 (AP-1) and/or nuclear factor-kappa B, which leads to reduced transcription of DIO1 [31] On the other side, increased expression of DIO3 is observed during inflammation. Higher expression of DIO3 by granulocytes and macrophages was observed in the inflammatory lesions of the spinal cord in experimental autoimmune encephalomyelitis [16] and in infiltrating neutrophilic granulocytes in response to an acute bacterial infection [15]. In addition, inflammation is characterized by low T3 levels [32], which may be somehow associated with increased expression of DIO3. With regard to our results, it is possible to suggest that DIO3 may be one of the inflammatory markers involved in the development and/or management of COPD, while DIO1 should rather be considered a determinant of TH levels in COPD.

As mentioned above, the levels of both DIO1 and DIO3 in depressive disorders have been recently investigated [20]. Based on the results obtained, differences in serum levels were confirmed. The concentration of DIO1 was significantly reduced, while DIO3 was significantly higher in the study group as compared to healthy controls. The latter results are in line with our findings presented in this study. This fact may further suggest that DIO3 increase may be associated with inflammation, as this process is also involved in the etiology of depressive disorders [33]. Inflammatory cells, such as neutrophils or macrophages, are increased in both COPD [4] and depression [34,35], and these cells are involved in the expression of deiodinases, particularly DIO3 [16]. This fact might be helpful in the explanation why DIO3 is increased in COPD patients. In addition, higher levels of DIO3 are linked with the presence and action of interleukins such as IL-1 and IL-6, i.e. the inflammatory molecules typically observed in COPD. The possible mechanism explaining an increase in DIO3 during inflammation is low oxygen levels, which leads to the absence of hydroxylation by hypoxia inducible factor - 1α (HIF-1α), resulting in an increase of HIF-1β and activation of gene transcription of DIO3. Moreover, nuclear factor-κ upactivation regulates DIO3 [31]. It cannot be excluded either that, for example, T3 reduction may be a consequence of increased T3 catabolism by DIO3 and increased production of reverse T3 from T4 [36]. DIO3 may be regarded as a factor affecting T3 levels by decreasing it. Low levels of T3 is one of the features of non-thyroidal illness syndrome (NTIS). The syndrome is observed in some cases of COPD [26] and is related to the severity of inflammation [37]. In contrast, our results are not explicit as we have observed higher levels of DIO1 in the patients with COPD, while NTIS is characterized by lower expression of this molecule [38]. We observed a correlation between DIO1, DIO3 – two opposite enzymes and BMI in patients. The results are in line with the literature as the relationship between body weight and thyroid status are complex [39]. Moreover, many hormonal and nutritional factors may affect the expression levels of DIOs, including fibroblast growth factors, transforming growth factor-beta (TGF-beta), epithelial growth factor (EGF) for DIO3 and glucocorticoids [40], and hepatocyte nuclear factor4α for DIO1 [41].

4.1. Limitations of the study

One of the limitations of our study is the fact that GLI 2012 data was not taken into account and patients were classified only according to the GOLD 2015.

5. Conclusions

To sum up, our study has demonstrated for the first time that peripheral serum levels of DIO1 and DIO3 may be related to COPD and/or the mechanism involved in the development and management of this disease. We can cautiously introduce and suggest that TH synthesis dominant molecules could be used as potential peripheral biomarkers in COPD. However, further experimental studies regarding DIO1 and DIO3 levels on a more diverse population of patients are needed. Investigating the expression and determining the importance of the molecules, and clarifying the possible influence of DIO1 and DIO3 on the pathogenesis and outcomes of COPD, as well as making comparisons with other known clinical parameters of the disease in question, are also worth performing.

Conflict of interest

The authors declare no conflict of interests.

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The authors contribution

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