Trakia Journal of Sciences, Vol. 12, Suppl. 1, pp 55-60, 2014

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

BRONCHIAL ASTHMA IN CHILDREN AND SERUM LEVELS OF STROMELYSIN 1 (MMP-3)

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ABSTRACT

Bronchial asthma (BA) among children is an important health issue worldwide, including Bulgaria. The prevalence is increasing although the reasons are poorly understood. The common characteristics of asthma include bronchial spasm, airway remodeling with variable narrowing, bronchial hyperresponsiveness, and airway inflammation. One of the key pathogenetic mechanisms is the disturbance of the protease/antiprotease balance, as the isoenzymes of matrix metalloproteinases (MMPs) family are shown to participate in the airway wall remodeling in BA. The MMP-3 (Stromelysyn 1) is found to be secreted by variety of inflammatory (monocytes/macrophages) and non-inflammatory cells (airway epithelial cells and lung fibroblasts).

The aim of this study was to evaluate the serum concentrations of MMP-3 in children with BA, to compare it with those of control individuals and to elucidate its possible role as a biomarker in BA in children. The levels of MMP-3 were measured by ELISA in the serum of 23 healthy controls (20 adults and 3 children under 17 years of age) and 24 asthmatic children (6 -17 years of age).

There was no difference in MMP-3 levels of the children with BA (mean of 3.05±3.96ng/ml) compared with adult controls (4.99±3.82ng/ml, p=0.307), or with healthy children (2.47±1.71ng/ml, p=0.880). When studied the asthmatic children, we observed a tendency for lower level of MMP-3 in younger children with BA (up to 12 years) than those above 12 years of age (2.06±1.95ng/ml vs. 5.47±6.34ng/ml, p=0.052) and in those with lower IgE levels (1.67±1.12 ng/ml vs. 4.88±6.10 ng/ml, p=0.077) .

According to our results we suggest that the serum MMP-3 levels could not be used as biomarker for BA in children. We suppose that the levels of MMP-3 and possibly the airway remodeling in asthmatic children might be affected by the age, as it was reported in a murine acute asthma model.

Key words: Bronchial asthma, children, MMP-3, IgE

INTRODUCTION

Bronchial asthma (BA) is chronic inflammatory disease of the airways characterized by variable recurring symptoms of airflow obstruction and bronchospasm (a result of epithelial desquamation, goblet cell hyperplasia, mucus hypersecretion and thickening of submucosa) (1, 2). The worldwide prevalence of the disease is increasing especially among children (3). Similar trend is observed also in Bulgaria (4).

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One of the major hypotheses for the pathogenesis of the disease is related to chronic inflammation and protease/antiprotease imbalance. The family of matrix metalloproteinases (MMPs) are secreted by inflammatory and non-inflammatory cells. MMPs are zinc-dependent proteinases which have an important role in many physiological and pathological conditions (wound healing, senescence, cancer, fibrosis and inflammation) due to their ability to degrade extracellular matrix (ECM), proteolytic modulation of biologically active proteins, and cell migration (5-7). MMPs are synthesized in non-active forms, zymogens. The activation can be done in several ways: stepwise, intracellular and cell surface-mediated mechanism. MMP activity is

ARCHIVES OF PHYSIOLOGY AND BIOCHEMISTRY, 2017
https://doi.org/10.1080/13813455.2017.1347690

Taylor & Francis
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ORIGINAL ARTICLE

The G allele of *MMP12 -82 A > G* promoter polymorphism as a protective factor for COPD in Bulgarian population

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ABSTRACT

Chronic inflammation and remodelling of the small airways are features related to chronic obstructive pulmonary disease (COPD). In the current study, we aimed to explore the possible role of *MMP12 -82 A > G* (rs2276109) promoter polymorphism in the development of COPD in a population from Bulgaria (167 patients with COPD and 119 control individuals).

The genotype and allele distributions differed significantly between COPD patients and controls ($p = .010$ and $p = .043$, respectively, χ^2 test). The genotypes containing at least one variant G allele (AA + GG) were more frequent in the control group than in patients (36.1% vs. 22.2%) determining 2.96-fold lower risk for COPD after adjustment for age, sex and smoking habits (OR = 0.338, 95%CI: 0.168–0.682, $p = .002$).

Our results suggest that carriers of genotypes with at least one copy of minor G allele of rs2276109 might have lower risk for COPD development, with no marked effect on the lung function and severity of the disease.

ARTICLE HISTORY
Received 23 April 2017
Revised 7 June 2017
Accepted 22 June 2017
Published online 7 July 2017

KEYWORDS
COPD; MMP; polymorphism; risk; case–control study

Introduction

In Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017, the definition of chronic obstructive pulmonary disease (COPD) states that "COPD is a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (GOLD 2017). Based on the spirometric parameters dependent on the airflow limitation during forced expiration, COPD is classified into four stages: GOLD I–IV (GOLD 2017). Airflow obstruction is determined as a reduction in the ratio of forced expiratory volume in 1 s (FEV1) over forced vital capacity (FVC). Lower than 70% ratio is considered as a hallmark of COPD (Hogg *et al.* 2004, Bidan *et al.* 2015).

Specific pathologic changes for COPD are found in the central airways, peripheral airways, lung parenchyma and pulmonary vasculature. Chronic inflammation and remodelling of the small airways and particularly of the terminal bronchioles are features related to the severity of disease (Chung and Adcock 2008). The remodelling is considered to be a result of the imbalance of endogenous proteinases and antiproteinases in the lung, which occurs due to genetic factors or altered activity and/or tissue levels of inflammatory cells and mediators.

Extracellular matrix (ECM) turnover is part of healthy tissue maintenance, with a continuous degradation of old proteins and synthesis of new ones. However, excessive ECM turnover may cause loss of lung function due to the structural changes in the organ (Sand *et al.* 2015). ECM consists of a large number of fibrous proteins, including collagens and elastin, but also glycoproteins and proteoglycans, as well as the components of basement membranes (Westergren-Thorsson *et al.* 2010). However, different repair processes may be active in different regions of the lung as the lung architecture, including the ECM scaffold, varies throughout the airway tree. (Rabe *et al.* 2007, Churg *et al.* 2009).

Matrix metalloproteinases (MMPs) are zinc-dependent proteinases, able to degrade ECM components, as well as to participate in the activation of cytokines and chemokines. They are released as inactive pro-enzymes and are activated by proteolytic cleavage of the N-terminal domain. Under normal conditions, their activity is low but increases during repair or remodelling processes and in several pathological conditions, including COPD. In mammals, 24 MMPs have been identified, divided into six groups, depending on their substrate specificity, sequence similarity and domain organisation (Demedts *et al.* 2005, Visse and Nagase 2003, Pardo *et al.* 2016).

Metalloelastase (MMP-12) is mainly expressed and secreted by macrophages and is essential for their migration, but human bronchial epithelial cells and smooth muscle cells may also produce MMP-12, especially in response to cigarette smoke. MMP-12 cleaves elastin, collagen type I, V and IV, gelatin, fibronectin, vitronectin, laminin, entactin, heparan

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BJMG 20 (2), 2017 • 59-66
DOI: 10.1515/bjmg-2017-0023

ORIGINAL ARTICLE

ASSOCIATION OF THE MMP7 –181A>G PROMOTER POLYMORPHISM WITH EARLY ONSET OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by decreased air flow and is associated with abnormal chronic inflammation in the airways and extensive tissue remodeling. Matrix metalloproteinase-7 (MMP7) is produced primarily by the epithelium of many organs, including the lungs. A functional MMP7 –181A>G (rs11568818) promoter polymorphism influences the binding of nuclear regulatory proteins modulating the transcription of the gene. In this study, we genotyped 191 patients with COPD for *MMP7* –181A>G single nucleotide polymorphism (SNP) and 215 control subjects using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and explored the role of that polymorphism as a risk factor for COPD. There were no differences in the genotype and allele distribution of the *MMP7* –181A>G SNP between the COPD patients and control groups ($p = 0.341$ and $p = 0.214$). However, the carries of the G allele (AG and GG genotypes), appeared to develop COPD significantly earlier than those with the AA genotype (61.01 ± 10.11 *vs.* 64.87 ± 9.00 years, $p = 0.032$). When the genotype distribution was studied only in the groups of patients ($n = 76$) and controls ($n = 106$) younger than 60 years, we found significantly higher frequency of the carriers of the G allele in COPD patients than in the controls, determining about a 3-fold higher risk for COPD [odds ratio (OR) –3.33, 1.36-8.14, $p = 0.008$ for GG, and OR = 2.91, 1.38-6.13, $p = 0.005$ for AG+GG]. Based on our results, the MMP7 –181A>G promoter variant may influence early development of COPD. This effect could be attributed to the increased production of the enzyme resulting in enhanced airway wall protein degradation and injury.

Keywords: Age; Chronic obstructive pulmonary disease (COPD); Matrix metalloproteinase-7 (MMP7); Polymorphisms; Risk.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to its severity in individual patients. Its pulmonary component is char-acterized by airflow limitation that is not fully reversible. The airflow limitation is associated with an abnormal inflammatory response of the lung to noxious particles or gases [1].

Smoking is one of the main risk factors for COPD, but since not all smokers develop COPD, as well as the fact that the disease often develops in middle age, it is suggested that other factors may play a role in the pathogenesis such as genetic factors [2]. Inhalation of cigarette smoke, organic and/or inorganic dust, chemical agents and particle matters increase the risk of developing COPD. The presence of these irritants, may lead to chronic inflammation and structural changes in the lung due to repeated injury and repair [3]. Pathological changes characteristic for COPD are found in the proximal airways, peripheral airways, lung parenchyma and pulmonary vasculature [4].

One of the main roles of the epithelial cells is to provide a barrier against pathogens and to release antimicrobial products. By producing chemoattractants and adhesion molecules, epithelial cells contribute to the migration of the inflammatory cells to injury sites [5,6]. Epithelial

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Biotechnology & Biotechnological Equipment, 2015
http://dx.doi.org/10.1080/13102818.2014.995411

ARTICLE; MEDICAL BIOTECHNOLOGY

Frequency of the common promoter polymorphism *MMP2 −1306 C>T* in a population from central Bulgaria

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(*Received 20 March 2014; accepted 11 November 2014*)

Matrix metalloproteinases (MMPs) are a family of highly homologous extracellular Zn^{2+}-dependent endopeptidases, also known as matrixins. MMP-2 (gelatinase A) and MMP-9 (gelatinase B) are considered to play a key role in a variety of physiological processes as well as in the development and progression of a vast majority of pathological conditions. Most of the genes encoding MMPs, including MMP-2, are highly polymorphic. One of the single nucleotide polymorphisms with functional activity in the promoter region of *MMP2* is the transition *MMP2 −1306C>T* (rs243865). The aim of the present study was to evaluate the genotype and allele frequencies of the common promoter polymorphism *−1306C>T* in *MMP2* in 75 individuals from central Bulgaria and to compare our results with those of other population studies. We found that 76.0% of the randomly enrolled individuals are carriers of the *CC* genotype, 17.3% of *CT*, and 6.7% of the *TT* genotype. The minor allele frequency (MAF) was 15.3%. Interestingly, the obtained genotype frequencies appeared to differ from those of some other Caucasian populations (USA – 55/38/7, MAF 26%; The Netherlands – 52.8/40.5/6.7, MAF 26.9%; Austria – 55.6/35.5/8.9, MAF 27.2%), but were closer to the values of the reported global genotype distribution (75.3/21.3/3.4, MAF 14%).

Keywords: MMP2; SNP; MAF; genotyping

Introduction

Multicellular organisms require an appropriate assembly of the extracellular matrix (ECM), which is essential for organizing tissues and organs and for functions and communications between cells. Coordinated changes in ECM composition (breakdown, synthesis and remodelling) are crucial for a variety of normal biological processes such as embryonic development, organ morphogenesis and ovulation.[1–4] On the other hand, the abnormal degradation of ECM proteins, either enhanced or decreased, occurs in a large number of pathological processes, such as cancer invasion and metastasis, rheumatoid arthritis, osteoarthritis, gastric ulcer, corneal ulceration, liver cirrhosis, fibrotic lung disease, atherosclerosis and chronic lung diseases.[1–8] The degradation of basement membrane (BM) and ECM proteins is accomplished by several proteolytic enzymes, which are released by a variety of cells. According to the amino acid residue or cofactor required for their activity, proteolytic enzymes can be divided into the following four groups: serine proteinases (e.g. plasminogen activators, PAs), lysosomal aspartyl and cysteine proteinases (cathepsins) and metalloproteinases, particularly matrix metalloproteinases (MMPs).[5–7,9]

MMPs are a large family of structurally related Zn^{2+}-dependent neutral endopeptidases, also known as matrixins. They are able to cleave virtually all protein components of the ECM and BM. Moreover, they can hydrolyse clotting factors, cell–cell and cell–matrix adhesion molecules, cell-membrane precursor forms of growth factors, growth-factor-binding proteins, growth factor receptors, other proteinases and proteinase inhibitors, as well as their own inactive zymogene forms.[7,10,11]

In humans, the family of MMPs consists of more than 20 members which differ in substrate specificity, regulation and interactions with other MMP family members and TIMPs (tissue inhibitors of metalloproteinases).[11–15] Depending on their substrate specificity, MMPs are classified into five main groups: collagenases (MMP-1, MMP-8 and MMP-13), stromelysins (MMP-3, MMP-10 and MMP-11), gelatinases (MMP-2 and MMP-9), matrilysins (MMP-7 and MMP-26) and membrane-type MMPs (MT-MMPs).[11–15] MMPs are active at physiological pH and are secreted as zymogens, which require extracellular activation.[10,11,14–16]

Gelatinases, MMP-2 (72 kDa type IV collagenase, gelatinase A) and MMP-9 (92 kDa type IV collagenase, gelatinase B), are principally involved in the degradation

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Article

Chronic Respiratory Disease

Chronic Respiratory Disease
1–8

DOI: 10.1177/1479972313504940
crd.sagepub.com

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Obesity in Bulgarian patients with chronic obstructive pulmonary disease

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Abstract

It has been well defined that obesity is strongly linked with several respiratory symptoms and diseases, but no convincing evidence has been provided for chronic obstructive pulmonary disease (COPD). In the current study, we aim to assess the possible prevalence of obesity in patients with COPD in a cross-sectional case–control study of individuals from the region of Stara Zagora, Bulgaria, and to explore whether the body mass has some effect on the lung function of COPD patients. The study included 158 patients with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) II, III, and IV stages) and 123 individuals unaffected by the disease (control). A higher frequency of obesity compared to the controls (20.3%) was observed in patients with COPD (29.1%, $p = 0.093$), especially in those with GOLD II stage (37.7%, $p = 0.009$). Prevalence of obesity was highest in COPD GOLD II, followed by GOLD III and IV stages ($p = 0.068$). When diabetes was considered as confounding factor, we found a significant prevalence of obesity in COPD patients than the controls with diabetes ($p = 0.031$). Interestingly, there was a statistically significant moderate positive correlation between the body mass index and forced expiratory volume in one second as a percentage of predicted value in the whole patients' group ($R = 0.295$, $p = 0.0002$) as well as in the subgroups of GOLD II ($R = 0.257$, $p = 0.024$) and GOLD III COPD ($R = 0.259$, $p = 0.031$).The results of our study propose that the increased body mass, particularly obesity is frequent comorbidity to COPD, especially to less severe diseases. Moreover, the results suggest that the higher body weight may provide some protection against the impairment of lung functions in patients with stable COPD.

Keywords

COPD, BMI, FEV_1, prevalence

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease, which is characterized by airway limitation that is not fully reversible.[1,2] COPD is a disease with systemic comorbid conditions including hypertension, diabetes mellitus, and cardiovascular diseases due to systemic inflammation. Chronic comorbidities affect health outcomes in patients with COPD, including mortality[3,4]

In the recent decades, obesity has significantly increased in society reaching epidemic proportions.[5,6] Based on the criteria of the World Health Organization, body mass index (BMI—the individual's body mass divided by the square of the height) can determines the following states: very severe underweight is indicated as less than 15.0 kg/m^2, severe underweight is from 15.0 to 16.0 kg/m^2, underweight is from 16.0 to 18.49 kg/m^2, normal is from 18.5 to 24.99 kg/m^2, overweight is from 25 to 29.99 kg/m^2, and obese is over 30 kg/m^2.[7]

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folia medica

Folia Medica 61(4): 512-21
DOI: 10.3897/folmed.61.e47745

Original Article

Possible Role of Serum Leptin as Biomarker in COPD

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Received: 04 Apr 2019 ♦ **Accepted:** 13 June 2019 ♦ **Published:** 31 Dec 2019

Citation: Zhelyazkova YA, Tacheva TT, Dimov DM, Vlaykova DG, Bivolarska AV, Vlaykova TI. Possible role of serum leptin as biomarker in COPD. Folia Med (Plovdiv) 2019;61(4):512-21. doi: 10.3897/folmed.61.e47745.

Abstract

Leptin is one of the adipokines shown to exert a significant effect in respiratory diseases, including chronic obstructive pulmonary disease (COPD).

The aim of the present study was to evaluate the possible role of serum leptin as biomarker in COPD.

The serum leptin levels were assessed in 58 patents with stable COPD and 21 controls applying ELISA method.

The leptin levels were higher, although not significantly, in COPD patients than in controls (221.52±24.28(SE) vs. 165.04±26.01 pg/ml, p=0.197). This tendency turned out significant when only females were compared (414.60±60.63 vs. 219.40±44.15 pg/ml, p=0.038). The levels of leptin were highly dependent on the BMI both in COPD patients (p<0.001) and in controls (p=0.024): they were the highest in obese individuals and decreased with reducing the BMI.

In the COPD group, women had significantly higher leptin levels than men (p<0.0001) independent of the BMI. The non-smoking patients had significantly higher leptin levels than ex-smokers (p=0.007) and current smokers (p=0.007). In patients with BMI above 25, several associations were observed: patients with mild COPD had higher serum leptin level than those with severe or very severe COPD (p=0.038); the leptin levels correlated positively with FEV_1% (r= 0.304, p=0.045) and FEV_1/FVC ratio (r= 0.348, p=0.021), and tended to correlate negatively with ABCD GOLD groups (Rho=-0.300, p=0.043) and with the CAT points (Rho=-0.258, p=0.091); the leptin levels below 300 ng/ml determined 4.08-fold higher risk for more severe COPD.

The results of our study confirm that the serum leptin levels depend significantly on the BMI and are interfered by gender and smoking habits. However, this adipokine cannot be used as a serum biomarker for distinguishing COPD patients, but its decrease might be associated with aggravation of the disease.

Keywords

biomarker, COPD, ELISA, leptin

Gender Differences of the Anthropometric Indices of Abdominal Obesity in Individuals with COPD

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Abstract. COPD is a chronic inflammatory lung disease which is associated with variety of co-morbidities, as the obesity and cardiovascular diseases (CVDs) are the most frequent. The aim of the current study was to explore the correlations of the age and BMI with the anthropometric indices associated with abdominal obesity in individuals with COPD and to explore the possible difference between the genders. Material and methods: This cross-sectional analysis included 851 citizens from the region of Yambol, Bulgaria. They were interviewed and blood pressure was measured during events organized at the World Diabetes Day, November 14, 2016-2018. One hundred and three of the individuals reported previous diagnosis of COPD. The further statistical analyses were performed only in this group of individuals applying SPSS 16.0 for Windows (SPSS Inc.). Results: Thirty three (32%) of the individuals with COPD were men with a mean age of 58.12 ±13.76 years, while the rest of 70 (68%) persons were women with a mean age of 66.70±10.73 years ($p=0.001$). The body mass index (BMI) correlated positively with the anthropometric indices associated with central obesity: the waist circumferences (WC, $r=0.601$, $p<0.0001$), the hip circumferences (HC, $r=0.619$, $p<0.0001$) and waist-to-hip ratio (WHR, $r=0.214$, $p=0.033$). The age correlated positively only with the WHR ratio in men ($r=0.390$, $p=0.025$), but not in women. When comparing the BMI between genders we did not observed difference ($p=0.802$). However when classified into groups according to the BMI, women were more frequently with normal weight (30.4%) and obese (33.3%) compared to men (25.8% and 16.1%, respectively), while men were more often with overweight than women (58.1% vs. 36.2%, $p=0.091$). Men had higher WC (99.23±11.40 cm, $p=0.080$) and especially WHR (0.922±0.067, $p<0.0001$) than women (94.17±14.50 cm and 0.855±0.084, respectively). According to the WHR the abdominal obesity was more frequently observed in men with COPD (78.8%) than in COPD women (58.6%. $p=0.045$). The measured high blood pressure was significantly associated with central obesity both in women ($p=0.038$) and in men ($p=0.035$).Conclusions: The results of our study confirm the positive correlation of the BMI with other anthropometric indices associated with abdominal obesity. Based on the results we could conclude that central obesity is more common in men than in women and determines a risk for higher blood pressure in patients with COPD.
Key words: COPD, abdominal obesity, BMI, WHR

INTRODUCTION

According to the Global Initiative for Chronic Obstructive Lung Disease (COPD), it "is a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airways and/or alveolar anomalies commonly caused by significant exposure to harmful particles or gases" [1]. COPD is a lung disease which is however associated with variety of co-morbidities, as the obesity and cardiovascular diseases (CVDs) are the most frequent [2,3]. The other frequent co-morbidities are peptic ulcer, obstructive sleep apnea, diabetes type 2, gastroesophageal reflux and osteoporosis. These pathological conditions contribute significantly to the course of COPD and lead to worsening of the prognosis [3].

Proceedings of the International Conference of Computational Methods in Sciences and Engineering 2019 (ICCMSE-2019)
AIP Conf. Proc. 2186, 110009-1–110009-4; https://doi.org/10.1063/1.5138028
Published by AIP Publishing. 978-0-7354-1933-9/$30.00

Harris et al. Respiratory Research (2016) 17:29
DOI 10.1186/s12931-016-0347-2

Respiratory Research

RESEARCH Open Access

A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma

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Abstract

Background: Quilizumab, a humanized IgG1 monoclonal antibody, targets the M1-prime segment of membrane-expressed IgE, leading to depletion of IgE-switched and memory B cells. In patients with mild asthma, quilizumab reduced serum IgE and attenuated the early and late asthmatic reaction following whole lung allergen challenge. This study evaluated the efficacy and safety of quilizumab in adults with allergic asthma, inadequately controlled despite high-dose inhaled corticosteroids (ICS) and a second controller.

Methods: Five hundred seventy-eight patients were randomized to monthly or quarterly dosing regimens of subcutaneous quilizumab or placebo for 36 weeks, with a 48-week safety follow-up. Quilizumab was evaluated for effects on the rate of asthma exacerbations, lung function, patient symptoms, serum IgE, and pharmacokinetics. Exploratory analyses were conducted on biomarker subgroups (periostin, blood eosinophils, serum IgE, and exhaled nitric oxide).

Results: Quilizumab was well tolerated and reduced serum total and allergen-specific IgE by 30–40 %, but had no impact on asthma exacerbations, lung function, or patient-reported symptom measures. At Week 36, the 300 mg monthly quilizumab group showed a 19.6 % reduction ($p = 0.38$) in the asthma exacerbation rate relative to placebo, but this was neither statistically nor clinically significant. Biomarker subgroups did not reveal meaningful efficacy benefits following quilizumab treatment.

Conclusions: Quilizumab had an acceptable safety profile and reduced serum IgE. However, targeting the IgE pathway via depletion of IgE-switched and memory B cells was not sufficient for a clinically meaningful benefit for adults with allergic asthma uncontrolled by standard therapy.

Trial registration: ClinicalTrials.gov NCT01582503

Keywords: Allergic asthma, Biomarkers, COSTA, IgE, M1 prime, Quilizumab, Exacerbations, FEV_1

Background

Asthma, a chronic inflammatory disorder of the airways, affects over 300 million people worldwide [1]. Some patients have persistent symptoms despite the use of steroids and other therapies. These patients are at the highest risk for future exacerbations and unscheduled use of healthcare resources [2].

Asthma is a heterogeneous disorder with distinct endotypes, the pathogenic cellular and molecular mechanisms that drive disease in different patient subgroups [3–6]. Allergic asthma is a hypersensitivity driven by the complex interaction of epithelial, dendritic, and type 2 innate lymphoid cells, leading to activation of $CD4^+$ T helper 2 (Th2) cells in response to allergen exposure [7]. Th2 cells produce interleukin (IL)-4, IL-5, IL-13, and other cytokines that promote immunoglobulin E (IgE) class switching of B cells, increased IgE synthesis by plasma B cells, and recruitment and activation of

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Trakia Journal of Sciences, No 2, pp 185-187, 2021

Available online at:
http://www.uni-sz.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2021.02.012

Review

COVID-19 AND BRONCHIAL ASTHMA

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ABSTRACT

Severe coronavirus disease-19 (COVID-19) presents with progressive dyspnea, resulting from acute lung inflammatory edema leading to hypoxia. Asthma has been cited as a potential risk factor for severe COVID-19 like other diseases that affect the respiratory tract. However, so far conflicting results have been published over the last few months and there is still no prove that there is a putative association between these two diseases. In the current mini-review we attempt to summarize the available information from the scientific literature concerning the relation of Bronchial asthma and the severity and clinical course of COVID-19 disease.

Key words: COVID-19, SARS-CoV-2, Bronchial asthma

Clinical symptoms in COVID-19 infection

Coronaviruses are the largest known positive-sense RNA viruses, with a wide range of hosts, and have serious negative effects on human and animal health. Coronaviruses known to infect humans, include low-pathogenic Coronaviruses (CoV-229E, CoV-NL63, CoV-OC43, and CoV-HKU1) causing mild to moderate illness and high-pathogenic coronaviruses that can lead to severe, potentially deadly diseases (1,2). In the twenty-first century, outbreaks with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have caused massive impacts on public health as well as socioeconomic aspects. Notably, the pandemic of coronavirus disease 2019 (COVID-19) caused by the novel Coronaviruse - Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) has posed a serious threat to global health since December 2019 (1,2).

It has been believed that SARS-CoV-2 spreads predominantly by droplets, aerosols, and contact transmission and can also be detected in stool, urine, and blood (1, 2). The majority of infected people have mild or no symptoms, but a proportion of patients display severe and rapid progression of the disease, leading to acute lung injury/acute respiratory distress syndrome and/or multiple organ failure (3, 4). The median incubation period is estimated to be 5.1 days, with 97.5% of symptomatic infections becoming evident within 11.5 days (5). The most common symptoms include fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%) (6). Laboratory examinations have shown that severe COVID-19 patients have decreased numbers of neutrophils, lymphocytes, and eosinophils and neutrophil-to-lymphocyte ratios, suggesting that abnormal, over activated immunity might be a possible mechanism (7).

Association of Bronchial asthma and COVID-19 infectious

In Bronchial asthma 80% of exacerbations are caused by respiratory viruses in children and half of such in adults. In response to respiratory viruses, people with asthma have increased clinical severity, bronchial hyperreactivity, impaired lung function and eosinophilic inflammation related to augmented Th2 or impaired Th1 or IL-10 responses (8)

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Trakia Journal of Sciences, No 3, pp 273-279, 2021

Available online at:
http://www.uni-sz.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2021.03.012

Review

"LONG COVID" - DEFINITION, SYMPTOMS, WHAT TO LOOK FOR AND HOW TO TREAT?

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ABSTRACT
"Long COVID," also referred to as "Long-Haul COVID or Post-COVID syndrome" is a condition where a person continues to experience symptoms of COVID-19 after their body has defeated the virus. On the bases of couple of clinical studies, we have attempted to describe the most common clinical symptoms that are present 12 weeks or more after having COVID-19, if these symptoms are not explained by another diagnosis. As can be seen, the long COVID is not an easy topic. There are many aspects to this issue because SARS-CoV-2 affects many organs in the human body. However, with the fast increase of data emerging from the vast variety of clinical studies that are currently underway, a better understanding will be obtained of how to treat patients with COVID-19 that have symptoms which have lasted for more than 12 weeks.

Key words: Long COVID ,SARS-CoV-2,Post COVID.

Definition

"Long COVID," also referred to as "Long-Haul COVID or Post-COVID syndrome" is a condition where a person continues to experience symptoms of COVID-19 after their body has defeated the virus [1-3]. Long COVID is a Post-COVID condition, which the Centers for Disease Control and Prevention (CDC) of the United States describes as "new, returning or ongoing health problems" caused by the disease more than a month after infection.

In the current review we are going to look into the long term effects of COVID-19, and potentially what we can do about them. The symptoms of long-term COVID-19 are complicated, and we will attempt to simplify them. There are a lot of terms that we use for "persistent COVID-19 symptoms":
- Long COVID or long haulers,
- Post acute sequelae of SARS-CoV-2 infection (PASC),
- Post acute COVID-19,
- Chronic COVID-19,
- Post COVID syndrome.

The definition for persistent COVID-19 symptoms is any symptoms that are present 12 weeks or more after having COVID-19, if these symptoms are not explained by another diagnosis [3].

The length of these symptoms dependents on whether or not, the patients have had severe COVID-19 whether or not, they were inpatient or outpatient. They can also depend on the type of symptoms. For instance fevers typically go away pretty quickly, whereas shortness of breath or fatigue can linger.

Clinical studies

The first study enrolled about 2000 health care workers in Sweden. In this study, there were compared SARS-CoV-2 positive patients with SARS-CoV-2 negative patients. When they looked at them 60 days post, they found that those that were SARS-CoV-2 positive - 26% of those had at least one symptom that was persistent versus just 9% in the SARS-CoV-2 negative. After 8 months that number had gone down from 26% to 15% but it was still lingering

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COMMON PROMOTER POLYMORPHISM *MMP12 -82 A>G* IN A POPULATION FROM CENTRAL BULGARIA.

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ABSTRACT

The matrix metalloproteinases (MMPs) are extracellular endopeptidases that cleave variety of proteins of the extracellular matrix (ECM), basal lamina, clotting factors, growth factor binding proteins, growth factor receptors. Some MMPs may hydrolyze zymogene forms of the members of the family, leading to their activation. MMP-12 (macrophage elastase) is a 22-kDa secretory proteinase that is predominantly expressed and secreted by activated macrophages. MMP-12 has a broad substrate specificity including elastin, fibronectin, laminin, vitronectin, type IV collagen, and heparan sulfate. Degradation of the basement membrane enables macrophages to penetrate injured tissues during inflammation.

The genes encoding *MMP12* is highly polymorphic. One of the functional polymorphisms is the A>G substitution at position -82 in the promoter region. This SNP influences the binding of the transcriptional factor AP-1 (Activator protein-1). AP-1 has greater binding affinity to the A allele which is associated with higher MMP-12 promoter activity *in vitro.*

The purpose of our study was to evaluate the genotype and allele frequencies of the common promoter polymorphism -82 A>G in *MMP12* in 119 (59 males and 60 females) individuals from central Bulgaria and to compare them with other Caucasian populations.

We found that 63.9% of the individuals were carriers of homozygous AA genotype, 35.3% were heterozygous (AG) and 0.8% were homozygous with the variant allele (GG). The obtained genotype frequencies appeared to differ from those of some other Caucasian populations from Europe: Netherlands- 72.2/25/2.8%; UK- 77/21/2%, and was closer to other (Germany- 64/34/2%).

Key words: MMP2, SNP, MAF, genotyping

INTRODUCTION

The extracellular matrix (ECM) is essential for organizing tissues and organs and for functions and communications of cells. The ECM preserves the geometry and structural integrity of various organs and tissues, but it is not only a scaffold that provides support for cells, but is further involved in cell-cell interactions, proliferation and migration (Zhong, Zhang et al. 2010; Lindner, Zietsch et al. 2012). Matrix metalloproteinases (MMPs) are a group of zinc dependent endopeptidases participating in the degradation of extracellular elements. Their substrates are marcomolecules of the ECM - different collagen types, proteoglycans, and glycoproteins. Due to their activity MMPs participate in many physiological and pathological processes in the body (Sternlicht and Werb 2001; Vihinen and Kahari 2002; Yoon, Cho et al. 2007; Kofla-Dlubacz, Matusiewicz et al. 2012). Moreover, they can splice and (in)activate cytokines and chemokines, thereby influencing the recruitment and function of inflammatory cells. They typically consist of a pro-domain and a catalytic domain. The latter contains a zinc ion in the active site, as well as a characteristic methionine loop. More than 20 MMPs have been identified in humans, which differ in substrate specificity, regulation and potential interactions with additional MMP family members and TIMPs. Some MMPs are anchored to the cell surface, whereas others are secreted in the extracellular space as inactive pro-enzymes and are activated by proteolytic cleavage of the N-terminal domain (Demedts, Brusselle et al. 2005; Fredriksson, Liu et al. 2006).

MMP12 -82 A>G Promoter Polymorphism in Bronchial Asthma in a Population of Central Bulgaria

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Laboratory Medicine 2018:00:1-8

10.1093/labmed/lmx085

ABSTRACT

A characteristic feature of inflamed lungs in bronchial asthma (BA) is airway remodeling. Due to limited information on this topic in the literature, we aimed to explore the possible role of polymorphisms in the promoter region of the macrophage elastase gene *MMP12* 82A>G (rs2276109) as a predisposing factor for BA in an ethnic Bulgarian population. Using restriction fragment length polymorphism analysis of polymerase chain reaction–amplified fragments (PCR-RFLP), we performed genotype analysis of 58 patients and 119 control individuals. We found statistically significant differences in the distribution of genotypes (P = .008) and alleles (P = .004) between patients and nonaffected controls. In the dominant model, carriers of the G allele genotypes had 3.6-fold lower risk for BA, compared with those with the AA genotype, after adjustment for age and sex (odds ratio [OR], –0.277; 95% confidence interval [CI], .12–.65; P = .003). The results of our study suggest that the variant G allele of the *MMP12* -82 A>G promoter polymorphism might be considered protective for development of BA in ethnic Bulgarian adults residing in central Bulgaria.

Keywords: bronchial asthma, MMP-12, polymorphism, risk, genotyping, PCR-RFLP

Abbreviations

BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; ECM, extracellular matrix; MMPs, matrix metalloproteinases; MMP-12, macrophage elastase; SNP, single nucleotide polymorphism; AP-1, activator protein–1; PCR-RFLP, restriction fragment length polymorphism analysis of polymerase chain reaction–amplified fragments; PCR, polymerase chain reaction; dNTP, deoxynucleotide; ANOVA, analysis of variance; LSD, least significant difference; HEW, Hardy-Weinberg equilibrium; TIMPs, tissue inhibitors of metalloproteinases; MALU, murine lung macrophage; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; IL, interleukin; NE, neutrophil elastase; …, nonapplicable; FEV1, forced expiratory volume: first second of forced breath; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval

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Bronchial asthma (BA) is a common chronic disorder of the airways that is characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammatory process.[1] The main pathological feature of BA is inflammation, in which many cells and cellular elements play a role.[2] Histological assessments of airways in patients with asthma, particularly patients with more severe disease, reveal injury to the epithelium and, often, loss of those cells. Because the airway epithelium is a rich source of inflammatory mediators and growth factors, injury to the epithelium may contribute to inflammation of the airways.[3] Airway smooth-muscle cells are also recognized as immunomodulators in asthma.[4]

The main immune cells infiltrating the lungs in BA are eosinophils; however, neutrophils and macrophages are also more numerous in the airways, especially in older patients with moderate to severe asthma and in asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome.[5-7]

MMP2 -1306C>T POLYMORPHISM IN PATIENTS WITH COPD

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ABSTRACT

The remodeling of the bronchial walls is an important process of the pathophysiology of COPD as the matrix metalloproteinase-2 (MMP-2) is shown to play an important role in this process.

The aim of the current study was to elucidate the possible role of *MMP2 -1306C>T* promoter polymorphism as a risk factor for COPD. We genotyped by PCR-RFLP 84 patients with COPD and 71 control individuals.

The genotype, but not the allele distribution, differed between COPD patients and controls (p=0.021 and 0.602, respectively). Carriers of the variant *T* allele genotypes *(CT+TT)* tended to have 1.64-fold higher risk for COPD (OR (Odds ratio) =1.64, 95% CI (confidence interval): 0.82-3.26, p=0.164) than those with *CC* genotype, as that risk was significant in the subset of individuals older than 65 years (OR=4.24, 95% CI:1.31-13.57, p=0.019). Patients with *T* containing genotypes *(CT+TT)* had a later onset of the disease (64.1±7.1 years) than those with a CC genotype (59.7±9.5 years, p=0.045). The risk for COPD of *T* carriers *(CT+TT)* was also significant in those individuals without diabetes as co-morbidity.

In conclusion, our results suggest that the carriers of T allele genotypes *(CT+TT)* of *MMP2 -1306C>T* SNP may have a higher risk for COPD in advanced age.

Keywords: *COPD, matrix metalloproteinases, polymorphism*

INTRODUCTION

The guidelines of Global Initiative for Chronic Obstructive Lung Disease (GOLD) define COPD as a disease state characterized by airflow limitation that is not fully reversible, usually progressive, and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases. Subsets of patients may have dominant features of chronic bronchitis and/or emphysema. The result is airflow obstruction that is not fully reversible (1). This pathology is associated with an airway inflammatory process characterized by an accumulation of inflammatory cells such as macrophages and neutrophils (2).

Systemic inflammation is often associated with COPD. There has been a growing recognition that co-morbidities such as cardiovascular disease, diabetes mellitus, cachexia, anemia, osteoporosis, or depression may be present in a greater proportion of

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Received: November 30, 2015
Accepted: February 22, 2016

The leukocyte telomere length, single nucleotide polymorphisms near *TERC* gene and risk of COPD

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction and is associated with chronic local and systemic inflammation and oxidative stress. The enhanced oxidative stress and inflammation have been reported to affect telomere length (TL). Furthermore, a number of SNPs at loci encoding the main components of the telomerase genes, *TERT* and *TERC* have been shown to correlate with TL. We aimed to explore the leukocyte TL and genotypes for single nucleotide polymorphisms, rs12696304 (C > G) and rs10936599 (C > T) near *TERC* in COPD cases and matched healthy controls using q-PCR technologies. Successful assessment of TL was performed for 91 patients and 88 controls. The patients had shorter TL (17919.36 ± 1203.01 bp) compared to controls (21 271.48 ± 1891.36 bp) although not significant ($p = 0.137$). The TL did not associate with the gender, age, spirometric indexes, smoking habits but tended to correlate negatively with BMI (Rho = −0.215, $p = 0.076$) in the controls, but not in COPD patients. The genotype frequencies of the SNPs rs12696304 and rs10936599 were compared between patients and controls and the odds ratios (OR) for developing COPD were calculated. The carriers of the common homozygous (CC) genotypes of the SNPs had higher risk for COPD, compared to carriers of the variants alleles (rs12696304 CG+GG *vs.* CC; OR: 0.615, 95% CI [0.424–0.894], $p = 0.011$ and for rs10936599 CT+TT *vs.* CC OR = 0.668, 95% CI [0.457–0.976], $p = 0.044$). Analysis on the combined effects of the *TERC* rs12696304 (C > G) and rs10936599 (C > T) genotypes, CC/CC genotype combination was associated with higher risk for COPD ($p < 0.0001$) and marginally lower FEV1% pr. in patients with GOLD II ($p = 0.052$). There was no association between the SNP genotypes and TL. In summary, our results suggest that COPD patients may have shorter TL, and rs12696304 and rs10936599 near *TERC* may affect the risk of COPD independently of TL.

Subjects Biochemistry, Molecular Biology, Respiratory Medicine

Keywords COPD, Telomeres, Telomerase, Polymorphism

Submitted 19 February 2021
Accepted 30 August 2021
Published 11 November 2021

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Academic editor
Nikolajs Sjakste

Additional Information and Declarations can be found on page 12

DOI **10.7717/peerj.12190**

INTRODUCTION

COPD is chronic inflammatory disease characterized by increased mucus production, shortness of breath and cough with sputum production. One of the big challenges in

Bulgarian Journal of Agricultural Science, 27 (No 5) 2021, 954–962

The relationship between the content of heavy metals Pb and Zn in some components of the environment, fishes as food and human health

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Abstract

Valkova, E., Atanasov, V., Vlaykova, T., Tacheva, T., Zhelyazkova, Y., Dimov, D. & Yakimov, K. (2021). The relationship between the content of heavy metals Pb and Zn in some components of the environment, fishes as food and human health. *Bulg. J. Agric. Sci., 27 (5)*, 954–962

The aim of the study was to establish the relationship between the content of Pb and Zn in the air, water, musculature of fish (*Cyprinus carpio* L.) and the blood serum of patients with and without COPD. The determination of the amounts of the studied heavy metals in drinking water and the blood serum of the patients was carried out by the method of atomic absorption.

The concentrations of Pb in the air do not exceed the requirements of Regulation 12 of 15.07.2010. The levels of lead found in the drinking water of the of Stara Zagora Town in the period June 2019 – July 2020 often approach the limit value determined by Regulation №9 of 16.03.2001 (0.01 mg/l). The established concentrations of zinc in the drinking water of the cities of Radnevo and Stara Zagora during the reported period are lower than the MAC of 4 mg/l defined in the normative documents.

The analysis of the data on our study of 2015 for the content of Zn in the musculature of common carp does not show an excess of the MAC set by the then current Regulation 31. The highest levels of zinc, which do not even approach the established norms were reached in muscle samples from fish delivered from Ovcharitsa Dam (8.09 mg/kg). With the lowest measured concentrations characterized Pastren Dam (2.69 mg/kg). Musculature samples from all studied water bodies do not exceed the MAC for lead, indicated in the then valid Regulation 31 and now the current Regulation №5 of the Bulgarian legislation and EC Regulation №1881 of 2006 with amendment from 2010 for determining the maximum permissible concentrations of some contaminants in foods. Although the values obtained are much lower than the regulated MAC, the highest concentrations are characterized carps from Lake Pastren Dam (0.04 mg/kg), and the lowest those from the Ovcharitsa Dam (0.01 mg/kg).

Keywords: lead; zinc; blood serum; COPD; musculature; carp; environment
Abbreviations: AAV – Annual average values; COPD – Chronic obstructive pulmonary disease;
DNA – Deoxyribonucleic acid; DOAS system – differential optical absorption spectroscopy – automatic sampling and analysis, averaged every hour; EEA – Executive Environment Agency; MAC – Maximum allowable concentration; PM10 – Particulate matter 10; RHI – Regional Health Inspectorate

Bulgarian Journal of Agricultural Science, 27 (No 5) 2021, 963–971

The relationship between the content of heavy metals Cd and Cu in some components of the environment, fish as food and human health

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Abstract

Valkova, E., Atanasov, V., Vlaykova, T., Tacheva, T., Zhelyazkova, Y., Dimov, D. & Yakimov, K. (2021). The relationship between the content of heavy metals Cd and Cu in some components of the environment, fish as food and human health. *Bulg. J. Agric. Sci., 27 (5)*, 963–971

The aim of the study was to establish the relationship between the content of Cd and Cu in the air, drinking water, musculature of fish (*Cyprinus carpio* L.) and the blood serum of patients with and without COPD. The amount of PM10 has highest values in 2017 (average annual value 25.2 μg/m^3).

The results regarding the amounts of cadmium in the air of the Stara Zagora region clearly show the absence of pollution. Determination of the amounts of the studied heavy metals in drinking water and the blood serum of the patients was carried out by the method of atomic absorption. The values of Cu, registered during the year-long study into the water of Stara Zagora and Radnevo are much lower than those adopted in Bulgarian legislation norms of 2 mg/l. The highest value of Cd is characterized by the drinking water in Stara Zagora Town from January 2020 (0.0047 mg/l), the value of which almost reaches the norm of 0.005 mg/l, defined in the normative documents. The cadmium concentrations measured during the same period in the drinking water of the Radnevo City are significantly below the accepted norms.

Concentrations of copper in musculature of common carp of from our study from 2015 were significantly lower than the norms in force at that time (Regulation №31 of 2004, laying down maximum levels for certain contaminants in foods). Ovcharitsa Dam (0.60 mg/kg) is characterized by the highest values, far below the norms regulated in the then current Regulation 31 (10 mg/kg). Minimum concentration was measured in the muscles of carp inhabiting the Pastren Dam (0.27 mg/kg). Against the background of extremely low values of the element cadmium in the muscles of the studied specimens of the species *Cyprinus carpio L*. the highest is the concentration measured in the samples from Opan Dam (0.0110 mg/kg), and the lowest in the samples from Pastren Dam (0.006 mg/kg). These concentrations are much lower than the MAC specified in the then active Regulation 31, as well as in the current Regulation №5 and Regulation 1881 (EU).

Keywords: cadmium; copper; blood serum; COPD; musculature; carp; environment
Abbreviations: AAV – Annual average values; COPD – Chronic obstructive pulmonary disease; DNA – Deoxyribonucleic acid; DOAS system – differential optical absorption spectroscopy – automatic sampling and analysis, averaged every hour; EEA – Executive Environment Agency; MAC – Maximum allowable concentration; PM10 – Particulate matter 10; RHI – Regional Health Inspectorate

обзори
Торакална Медицина
Том IX, бр.3
септември 2017

ПРОУЧВАНЕ РОЛЯТА НА НЯКОИ АДИПОКИНИ – ЛЕПТИН И АДИПОНЕКТИН ПРИ ХОББ

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Резюме

Хроничната обструктивна белодробна болест (ХОББ) е често срещано предотвратимо и лечимо заболяване, което се характеризира с персистиращи респираторни симптоми и ограничение на въздушния поток, дължащо се на аномалии на дихателните пътища и/или алвеолите, обичайно причинени от значителна експозиция на вредни частици или газове. Без съмнение ХОББ е възпалителна болест. Абнормен възпалителен отговор се наблюдава не само на белодробно ниво при пациенти с ХОББ, но и на системно ниво. Цитокините, произвеждани от белодробни клетки като TNF-α, IL-6, IL-1β, могат да достигнат системното кръвообращение и да допринесат за активиране на нови клетки, преминавайки през белия дроб. Произходът на системното възпаление не е ясен. Изследванията в областта на възпалението при ХОББ са обещаващи. Надеждите са свързани с откриване на нови подходи за лечение, насочени към специфичните популации пациенти, идентифицирани от клиничния фенотип или биомаркери. Такива биомаркери могат да бъдат белтъчните медиатори, синтезирани и секретирани от мастната тъкан, адипокините, и по-специално лептинът и адипонектинът.

Целта на настоящия обзор е да бъде обобщена научна информация относно ролята на мастната тъкан като източник на адипокини, сигналните пътища на действие на някои от тях и да бъдат представени резултати от изследвания, доказващи ролята на два от основните адипокини, лептин и адипонектин, в развитието, прогресията и състоянията на екзацербация при ХОББ. В допълнение са представени доказателства за ролята на серумните нива на лептина и адипонектина като потенциални биомаркери при това хронично възпалително заболяване на белия дроб.

Ключови думи: ХОББ, лептин, адипонектин, системно възпаление

Вариабилност на симптомите при ХОББ през денонощието

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ХОББ е хронична, прогресивна болест със значителна честота, водеща до инвалидизация и висока смъртност. Влошаването на белодробната функция при ХОББ се придружава с нарастване на симптоматиката.

Настоящият обзор прави преглед на последните клинични изпитвания и доказателства за наличието на значителна вариабилност на симптоматиката на ХОББ и възможностите за бързо и успешно повлияване на сутрешните симптоми.

Ключови думи: *ХОББ, вариабилност на симптомите, сутрешна симптоматика, сутрешни активности*

Variability of COPD symptoms during the day

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Summary

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive disease leading to substantial morbidity and high mortality. The deterioration of lung function in COPD patients is accompanied by increase of symptoms.

The current review is aimed to discuss the latest clinical trials and evidence about the existence of significant variability of the symptoms of COPD and possible therapeutic approaches for fast and efficient management of morning symptoms.

Key words: *COPD, symptoms variability, morning symptoms, morning activities*

ХОББ е хронична прогресивна болест със значителна честота, водеща до инвалидизация и висока смъртност[1,2]. При ХОББ има наличие на белобробен и извънбелодробен компонент, които допринасят за тежкия характер на болестта при определени пациенти. Белодробният компонент на ХОББ се характеризира с ограничение на въздушния поток в дихателните пътища, което не е напълно обратимо дори и след лечение. Обикновено това ограничение е прогресиращо и се дължи на възпалителна реакция на белите дробове към вредни частици или газове. Клиничната изява включва хронична кашлица, прогресираща диспнея, продукция на храчки и намален физически капацитет[2,3]. При ХОББ често се наблюдават епизоди на остро влошаване на тези симптоми (екзацербация).

От морфологична гледна точка белодробният компонент на ХОББ включва възпалени малки дихателни пътища (*обструктивен бронхиолит*) и разрушен паренхим (*емфизем*).

Извънбелодробният компонент на ХОББ е свързан с разгърналия се в целия организъм абнормен възпалителен процес, вероятно започнал от белите дробове. В този смисъл ХОББ днес се приема за *системен възпалителен процес*. Системното възпаление се проявява като кахексия, загуба на скелетна мускулатура, повишен риск от развитие на сърдечно-съдови болести, анемия, остеопороза и депресия[4].

ХОББ се представя с малка вариабилност в симптоматиката за разлика от бронхиалната астма, за която е прието, че е вариабилно заболяване с често влошаване през нощните часове и сутрин. В научната литература има доказателства за циркадна вариабилност на инспираторния капацитет (IC), форсирания експираторен обем за 1 сек (FEV_1) и върховия експираторен дебит (PEF) при ХОББ[1, 5-7]. Това е дало основание на редица изследователи да проведат изследвания при пациенти с ХОББ за отчитане влиянието на заболяването върху обичайните им дневни и сутрешни активности, както и за определяне на евентуалната вариабилност на симптомите (сезонна, седмична и дневна)[1, 8-10].

Вариабилност на симптомите при ХОББ

Традиционно ХОББ се смята за непрекъснато прогресиращо заболяване, при което влошаването на белодробната функция се придружава с нарастване на симптоматиката, както и с поява на екзацербации. Но съвременни проучвания показват, че симптомите в периодите извън екзацербация не са постоянни.

В проучване, включващо 803 пациенти с ХОББ от Европа и САЩ, от които 289 с тежък ХОББ, се установява, че сутринта е най-проблемното време от денонощието при пациенти с ХОББ (при 37% от всички пациенти с ХОББ и 46% от пациентите с тежък ХОББ)[1].

Кашлицата с отделяне на храчки, персистиращата кашлица, недостигът на въздух и лесната уморяемост са най-честите симптоми, съобщавани сутрин. При пациентите с тежък ХОББ недостигът на въздух, кашлицата с отделяне на храчки и персистиращата кашлица са най-често съобщаваните симптоми (78%, 63% и 60%,

НОВИ ПОДХОДИ ПРИ ФАРМАКОЛОГИЧНОТО ЛЕЧЕНИЕ НА ХОББ

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NEW APPROACHES TO PHARMACOLOGICAL TREATMENT FOR COPD

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lungs with a significant social effect. COPD is a preventable and curable disease. After the establishment of COPD, efforts are aimed at relieving symptoms; prevention of disease progression; improving tolerance to physical burden; improving the health status; prevention and treatment of complications; prevention and treatment of exacerbations; reducing mortality and prevention or minimization of the side effects of treatment. Pharmacological treatment of COPD aims to control and prevent symptoms, reduce the frequency and severity of exacerbations, improve health status and tolerance to exercise.

This review aims to overview the new approaches to pharmacological treatment of COPD. Attention is paid on cellular signaling pathways, cell processes and molecules being therapeutic targets for the development of the new groups of therapeutic agents.

Keywords: *COPD, pharmacological therapy, cell signaling pathways, antioxidants, proteinases.*

Въведение

Хроничната обструктивна белодробна болест (ХОББ) е хронично възпалително заболяване на белите дробове със значим социален ефект. При ХОББ се наблюдава необратимо намаляване (влошаване) на белодробната функция. Емфиземът, хроничният бронхит с обструкция на бронхите и заболяване на малките въздухоносни пътища са различни фенотипи на ХОББ, но повечето пациенти показват комбинация от тях (Димитров 2000; MacNee 2005; Костов 2007; Barnes 2010; Костов, Османлиев et al. 2010).

ХОББ е комплексно заболяване, чието развитие и прогресия се определя от фактори на околната среда, генетични фактори и взаимодействието помежду им. ХОББ е предотвратима и лечима болест с някои значими извънбелодробни ефекти, които могат да допринесат за тежкия характер на заболяването при определени пациенти (Agusti, Noguera et al. 2003; Andreassen and Vestbo 2003; Barnes 2010; Osthoff, Jenkins et al. 2013).

След установяване на ХОББ, усилията са насочени към облекчаване на симптомите; предотвратяване прогресията на болестта; подобряване на поносимостта към физически натоварвания; подобряване на здравния статус; предотвратяване и лечение на усложненията; предотвратяване и лечение на екзацербациите; намаляване на смъртността и предотвратяване или минимализиране на страничните ефекти от лечението (Димитров 2000; Костов, Османлиев et al. 2010). Тези цели могат се постигат чрез приложение на програма за лечение на ХОББ, включваща 4 компонента: 1)Оценка и мониториране на болестта; 2)Намаляване на рисковите фактори; 3)Лечение на стабилната ХОББ; 4)Контрол на екзацербациите.

ХРОНИЧНА ОБСТРУКТИВНА БЕЛОДРОБНА БОЛЕСТ И НАРУШЕНИЯ В СКЕЛЕТНАТА МУСКУЛАТУРА

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CHRONIC OBSTRUCTIVE PULMONARY DISEASES AND DISORDERS IN SKELETAL MUSCLE

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease of the lungs, but there are many systemic manifestations, of which perhaps the most important is the muscular dysfunction. Muscle dysfunction highly contributes to the reduction of physical capacity, the benefits of treatment and is an independent predictor of morbidity and mortality. Discovering the intimate molecular mechanisms leading to muscle dysfunction is key to developing new and changing of the old therapeutic strategies to combat muscle dysfunction in COPD.

The aim of this review is to summarize the knowledge on pathophysiological disorders of the peripheral muscles in COPD with special attention to skeletal muscle atrophy, the histological changes associated with redistribution of fiber types, changes in muscle bioenergy and blood flow on capillary level. A special place is taken by the information on pathogenic mechanisms of muscle dysfunction as imbalance of turnover of proteins, impaired nutrition of cells, reduced physical load on the muscles, use of systemic corticosteroids, tissue hypoxia and hypercapnia, inflammation, oxidative/nitrogen stress and mitochondrial impairment.

Keywords: *COPD, systemic effects, muscle dysfunction*

Въведение

Хроничната Обструктивна Белодробна Болест (ХОББ) е хронично възпалително заболяване на белите дробове, което засяга над 280 милиона души в цял свят, нареждайки се на четвърто място по смъртност като взема над 2,75 милиона жертви годишно (de Marco, Accordini et al. 2004; Rabinovich and Vilaro 2010). Счита се че до 2020-та година ще е третата причина за смъртност (Bruno and Valenti 2012).

Необратимата обструкция на въздухоносните пътища дефинира заболяването, но степента на обструкцията измерена с форсирания експираторен обем за първата секунда от издишването (FEV1) не винаги корелира с тежестта на симптомите и свързаното със здравето качество на живот и преживяемост на пациентите годишно (Rabinovich and Vilaro 2010).

ХОББ до голяма степен повлиява здравният статус и функционалният капацитет на пациентите. ХОББ не е само белодробно заболяване, а има и много системни прояви, от които вероятно най-важната е мускулната дисфункция (Andreassen and Vestbo 2003; Rabinovich and Vilaro 2010). Мускулната дисфункция активно допринася до намаляване на физическият капацитет, ползите от лечението и е независим предиктор на заболеваемостта и смъртността. Вникването в молекулярните механизми водещи до мускулната дисфункция е

ОСТЕОПОРОЗА И ХОББ

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OSTEOPOROSIS AND COPD

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease, wherein there is present extrapulmonary effects on distant organs, so-called systemic effects and comorbidities. Skeletal muscle dysfunction, eating disorders, including weight loss, cardiovascular complications, metabolic complications and osteoporosis are well recognized diseases associated with COPD. Osteoporosis is characterized by decreased skeletal resistance to impairment of bone microarchitecture, leading to decreased bone mass and reduced mineral content.

In this paper it is presented a review of the current data about the relationship between COPD and osteoporosis, about the pathophysiology and mechanisms of development of osteoporosis, and about the risk factors and treatment approaches of osteoporosis in patients with COPD.

Keywords: *COPD, osteoporosis, pathophysiology, risk factors*

Въведение

Хронична обструктивна белодробна болест (ХОББ) е хронично възпалително белодробно заболяване, при което има налични екстрапулмонални ефекти върху отдалечени органи, така наречените системни ефекти и съпътстващи заболявания. Скелетната мускулна дисфункция, хранителни нарушения, включително загуба на тегло, сърдечно-съдовите усложнения, метаболитни усложнения, и остеопороза са добре признати заболявания, асоциирани с ХОББ. Тези извънбелодробни ефекти увеличават тежестта, усложненията и смъртността при ХОББ и поради това следва да бъдат активно търсеше, оценени и лекувани (Choudhury, Rabinovich et al. 2014).

Дефиниция и епидемиология на остеопорозата

Остеопорозата се характеризира с намалена скелетна резистентност към нарушения на микроархитектурата на костите, водещи до намалена костна маса и понижено съдържание на минерали. Последствията са костна чупливост и повишен риск от фрактури. Дефинира се като плътност на минералите в костта под 2.5 SD (T- score < -2.5) измерена с костна денситометрия. Фрактури, свързани с остеопорозата по-често се появяват в гръбнака, бедрените кости и китките. Остеопорозата е преклинично състояние и се дефинира като T-score между -2.5 и -1. Повишената честота на костните нарушения се увеличават с възрастта: счита се че, 8-18% от жените и 5-6% и мъжете >50 години имат остеопороза (Franssen, Wouters et al. 2002). Тъй като ХОББ е болест възникваща през втората половина от живота това съпътстващо заболяване е очаквано. Респираторните усложнения на остеопорозата са още по изразени при ХОББ защото е намален функционалния капацитет, което увеличава

Новите възможности за използване на FOSTER след MART2

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Резюме

Използването в клиничната практика на beclomethasone dipropionate /formoterol (Foster) за поддържащо лечение на Бронхиланата астма от пулмолозите и алерголозите от цял свят е успешно. Приемането на комбинацията beclometasone dipropionate–formoterol в екстрафайн формула (hydrofluoroalkane formulation) - FOSTER плюс Salbutamol за овладяване на остро появили се симптоми в режим „терапия при нужда" (релийвър) прави възможно лечението на Бронхиална астма с по-ниска еквивалентна кортикостероидна доза в сравнение с други съпоставими налични комбинации. Клиничната ефективност на комбинацията в pMDI на ниска-доза екстрафайн beclometasone–formoterol в режим на поддържаща терапия е довела до предположението, че подобна ефективност би могло да бъде постигната, ако тази комбинация бъде използвана и като релийвър.

Клиничното изпитване NCT0086192 представлява мултинационално, мултицентрово, рандомизирано, двойно-сляпо с две паралелни групи активно контролирано изпитване, проведено с цел проучване на въпроса дали инхалираната фиксирана комбинация в екстрафайн форма на beclometasone 100 μg и formoterol 6 μg е по-ефективна при прилагане както като поддържащ, така и като релийвър медикамент в сравнение с прилагането ѝ като поддържаща терапия с добавяне на кратко-действащ бета2-агонист (Salbutamol) при нужда.

Резултатите от клиничното изпитване недвусмислено доказват превъзходството на прилагането на extrafine beclometasone- formoterol като поддържащ и релийвър медикамент за редукция на риска от екзацербации в сравнение с extrafine beclometasone-formoterol като поддържащ и Salbutamol като релийвър медикамент. Тези резултати се дължат до голяма степен на по-голямата периферна депозиция на екстрафайн формата като резултат от по-малкия размер на частичките.

В заключение, въз основа на резултатите от описаното клинично изпитване и други предходни изпитвания, се потвърждава предимството на използване на инхалаторен кортикостероид с дълготрайстващ бета2-миметик с бърз ефект като поддържащ и релийвър медикамент при пациенти със среднотежка и тежка бронхиална астма.

New opportunities for the use of Foster after MART2

Abstract

The combination beclomethasone dipropionate /formoterol (FOSTER) given as maintenance of Bronchial asthma is successfully used in clinical practice by pulmonologists and allergists worldwide. The application of the combination of beclometasone dipropionate–formoterol in an extrafine formulation (hydrofluoroalkane formulation) plus salbutamol as a reliever makes the therapy of Bronchial asthma with tower equivalent corticosteroid doses compared to the other two existing combination of an inhaled corticosteroid and a long-acting β2 agonist. The clinical efficiency of the combinations in a single pressurised metered-dose inhaler (pMDI) of a low-dose extrafine beclometasone-formoterol as maintenance has supported the notion that simial efficiency might be achieved when that combination is given as both as maintenance and reliever.

The clinical trial assigned as NCT00861926 is a multinational, multicentre, doubleblind, randomised, parallel group, active-controlled trial, performed to investigate whether the inhaled fixed combination of extrafine formulation of beclometasone 100 μg and formoterol 6 μg per one inhalation twice daily is more effective when given as maintenance and reliever in comparison to the application of those combination as maintenance with a short-acting β2 agonist (Salbutamol) for relief of symptoms.

The results of the clinical trial clearly showed the superiority of giving the extrafine beclometasone-formoterol as maintenance and reliever for reducing the risk of exacerbations compared with the extrafine beclometasone-formoterol as maintenance and Salbutamol as reliever. The results might be attributed in large part to the higher drug deposition in the peripheral airways of the extrafine formulation as a consequence of the smaller particle size.

In conclusion, based on the results of the described clinical trial and of previously reported trials, there is a confirmation of the advantage of the use of a single inhaled corticosteroid and a rapid-onset, long-acting β2 agonist combination for maintenance and relief in patients with moderate to severe asthma.

Използването на Foster (Beclomethasone/formoterol) за поддържащо лечение на Бронхилана астма (БА) е успешно в клиничната практика на пулмолозите и алерголозите от цял свят. Във връзка с широко дискутираната, включително и в GINA възможност за едновременно използване на инхалаторен кортикостероид (ИКС) и дълго действащ бета2-агонист (ДДБА) както при поддържаща терапия така и за „спасителен" медикамент при нужда (релийвър), бе проведено Клинично изпитване с код NCT0086192. Това клинично изпитване започна през март 2009 и бе спонсорирано от *Chiesi Farmaceutici S.p.A.* Резултатите от него бяха публикувани в мартенския брой на ***Lancet Respir Medicine*, 2013**[1].

Международното ръководство за терапия на БА (GINA) препоръчва комбинацията от ИКС и ДДБА с добавяне на Salbutamol като релийвър за лечението на пациенти, които не са адекватно контролирани само с ИКС[2]. Всички налични комбинации от ИКС и ДДБА имат подобни ефекти при пациенти със средно тежка и тежка астма когато са приемани с кратко действащ бета2-агонист[3, 4].

Приемането на комбинацията *beclometasone dipropionate–formoterol* във екстрафайн формула (hydrofluoroalkane

Нови изследвания в патогенезата и терапията при бронхиална астма

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Бронхиалната астма (БА) е често срещано и потенциално сериозно хронично заболяване, предизвикващо значителна тежест на пациентите, техните семейства и общността. БА предизвиква респираторни симптоми, намалена активност и обостряния, които понякога изискват спешна медицинска помощ и могат да бъдат фатални[1].

БА се проявява със свирене, затруднено дишане, стягане в гърдите и кашлица, които варират в тяхната поява, честота и интензитет. Те са асоциирани с ограничение на експираторния въздушен поток, т. е затруднено издишване, дължащо се на бронхоконстрикция, ремоделиране на бронхите и увеличено отделяне на мукус. Някои вариации на ограничение на въздушния поток могат да се наблюдават при хора без БА, но прерастват в астма[1].

БА е сериозен здравен проблем, засягащ всички възрастови групи, с нарастващо превалиране в много развити страни. БА се среща при 5-10% от Европейската популация или 23.4 милиона души, от които 7 милиона деца. В САЩ това заболяване засяга приблизително 26 милиона души. БА засяга приблизително 300 милиона души в световен мащаб. Астмата и е най често срещаното заболяване в детска възраст[2].

За щастие, БА може да бъде ефективно лекувана и повечето пациенти могат да постигнат добър контрол на болестта[1].

Патогенеза

Патогенезата на болестта е комплексна и включва възпаление на дихателните пътища (ДП), интермитентна обструкция и бронхиална хиперреактивност (БХР). Механизмът на възпаление при БА може да бъде остър, подостър и хроничен, а развитието на оток и мукусна секреция допринасят за обструкцията и БХР. Налице е инфилтрация на бронхите с различни видове мононуклеарни клетки, еозинофили (ЕО), мукусна хиперсекреция, десквамация на епителa, гладкомускулна хиперплазия и ремоделиране на ДП.

БХР при астма е в отговор на многобройни екзогенни и ендогенни стимули. Механизмите включват директна стимулация на гладката мускулатура от медиатори и индиректна стимулация от немиелинизирани сензорни неврони. Степента на БХР обикновено корелира с клиничната тежест на астмата[2].

Някои от главните клетки, идентифицирани във възпалението, са: мастоцити, еозинофили, макрофаги, активирани Т-лимфоцити и епителни клетки. Възпалението при астма може да бъде представено като загуба на нормален баланс между две противоположно действащи популации Т-лимфоцити: Th1 и Th2 (CD4+). Th1 клетките продуцират провъзпалителни цитокини като IL-2, INF-γ и др. В контраст Th2 клетките генерират IL-4, IL-3, IL-5, IL-9, IL-13, които могат да медиират алергично възпаление. Ключови медиатори са също еотаксин, NO, левкотриени. Проучване на Gauvreau et al. намира, че IL-13 има роля в алерген-индуцирания отговор[3].

Левкотриените (ЛТ, LT) имат централна роля в патогенезата на астмата. Аеробните упражнения с нисък или умерен интензитет намаляват възпалението при астмата в условията на клинични проучвания и експериментални модели. Проведено е проучване сред мишки, което показа, че аеробните физически упражнения водят до намаление на ЕО, неутрофилите, лимфоцитите и макрофагите в БАЛ, както и ЕО, лимфоцитите и макрофагите в стените на ДП. При мишките с астма, които извършват физически аеробни упражнения, се наблюдава намаление на нивата на IL-5, IL-13, CysLT (цистеинил-левкотриен) и LTB_4 в БАЛ. Установена е по-ниска експресия на молекулите от левкотриеновата каскада, ензима LTC_4 синтаза и рецептор 2 на LTB_4 (LTB_2) от перибронхиалните левкоцити и епителa на ДП[4].

Роля на мастната тъкан и адипокините при бронхиална астма

Напоследък на мастната тъкан се отдава все по голямо значение в патогенезата на БА[5]. Има доказателства,

INSPIRO
СПИСАНИЕ ЗА РЕСПИРАТОРНА МЕДИЦИНА И ВДЪХНОВЕНИЕ

Тройна инхалаторна терапия при пациенти с ХОББ

Брой № 4 (47) / септември 2018, Тройна инхалаторна терапия при ХОББ

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Резюме

Общоприето е, че ХОББ е важен здравен проблем поради високата заболеваемост, ежегодното нарастване на новите случаи и поради високите лични, социални и икономически разходи. Подобряване качеството на живот и превенцията от екзацербации (ЕКЦ) е ключова терапевтична цел при пациенти с ХОББ.

Според препоръките на GOLD 2018, при симптоматични пациенти с ЕКЦ в предходния период от 12 месеца фармакологичната терапия на ХОББ се базира основно на използването на инхалаторни лекарства: дългодействащи бронходилататори (дългодействащи мускаринови антагонисти [ДДМА], дългодействащи β2 агонисти [ДДБА], или комбинация от тях) с или без инхалаторен кортикостероид (ИКС).

Инхалаторната тройна терапия, включваща ИКС, ДДБА и ДДМА, е широко прилагана в практиката, като в последните години се натрупаха данни от клинични изпитвания, показващи преимуществата ѝ в сравнение с други препоръчвани терапии при оценяване на съотношението полза/риск при пациенти с ХОББ.

За прилагане е разработен единичен инхалатор за тройна терапия в *екстрафайн формула* (т.е. с частици под 2 μm), включваща ИКС beclometasone dipropionate (BDP), ДДБА formoterol fumarate (FF) и ДДМА glycopyrronium bromide (GB).

В настоящия преглед са представени резултатите от три основни клинични изпитвания: **TRILOGY**, **TRINITY** и **TRIBUTE**, проведени със симптоматични ХОББ пациенти и с ЕКЦ в предходния 12-месечен период, при които *недвусмислено е показано, че инхалаторната екстрафайн тройна терапия, включваща BDP/FF/G, прилагана с единичен инхалатор (pMDI), се асоциира със статистически значимо понижение на риска от средно тежки –тежки ЕКЦ, без нарастване риска от странични събития, включително пневмонии, в сравнение с други терапевтични подходи като монотерапия с ДДМА или комбинирани терапии ИКС/ДДБА или ДДБА/ДДМА.*

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Biotechnology & Biotechnological Equipment, 2014
Vol. 28, No. 5, 904–910, http://dx.doi.org/10.1080/13102818.2014.947694

ARTICLE; MEDICAL BIOTECHNOLOGY

Investigation of the role of *MMP3 -1171insA* polymorphism in cutaneous malignant melanoma – a preliminary study

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(*Received 20 March 2014; accepted 20 June 2014*)

Coetaneous malignant melanoma is the most aggressive cancer of the skin with a high rate of mortality worldwide. Degradation of basement membranes and extracellular matrix is an essential step in cancer invasion and metastasis. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play key roles in this step. MMP-3 also called stromelysin-1 was one of the first proteinases found to be associated with cancer. In the gene of MMP-3 *(MMP3*), an insertion/deletion of an A nucleotide at position -1171 in promoter region has been identified and shown to effect the expression activity of the gene.

The present study was conducted to investigate the relation of *MMP3 -1171insA* polymorphism with skin malignant melanoma risk in a pilot case-control study of Bulgarian patients (n = 26) and unaffected controls (n = 172).

The genotypes of controls and melanoma patients were in Hardy-Weinberg equilibrium. The results showed no statistically significant difference both in genotype and allele frequencies of *MMP3 -1171insA* polymorphism between melanoma patients and healthy controls either in crude analyses (p = 0.360 and 0.790, c2-test) or after adjustment for age and sex. The comparison of some clinical characteristics between the patients with different genotypes showed a trend for longer survival of patients with *6A/6A* genotype compared to the carriers of *5A* allele (*5A/5A+5A/6A* genotypes, p = 0.118, Log rank test).

The results of our current preliminary study do not provide evidence for the role of the promoter polymorphism *-1171insA* in *MMP3* as a risk factor for development of coetaneous melanoma, but suggest its implication in progression of the diseases.

Keywords: skin malignant melanoma; MMP3; genetic predisposition; survival

Introduction

Malignant melanoma of the skin is a peculiar neoplasm with an unpredictable clinical course: it may remain silent for many years after its primary occurrence or it may behave in a very aggressive way and metastasize early.[1] Tumourogenesis in general, and melanoma development particularly, is a complex multi-step process accompanied by genetic and epigenetic changes which lead to acquisition of ability of cancer cells to invade the surrounding tissues and to disseminate into distant organs. These processes require enhancing of tumour angiogenesis and degradation of basement membranes and extracellular matrix, which are assisted by the increased expression and activity of matrix proteinases, such as plasminogen activators (t-PA and u-PA), cathepsins (cysteine or aspartyl proteinases) and matrix metalloproteinases (MMPs).[2]

MMPs are a large family of zinc-dependent natural endopeptidases that can degrade virtually all extracellular matrix components. At present, the family of MMPs consists of more than 20 members (currently, 23 in humans), which differ in substrate specificity, regulation and potential interactions with additional MMP and TIMP family members.[3–6] MMPs can be divided into the following five groups: collagenases (MMP-1, -8 and -13), stromelysins and stromelysin-like MMPs (MMP-3, -10, -11, -12), gelatinases (MMP-2 and -9), matrilysins (MMP-7 and -26) and membrane-type matrix metalloproteinases (MT-MMPs, MMP-14, -15, -16, -24, -17, -25).[6–10].

Gene expression of metalloproteinases is detected in particularly all cell types such as fibroblasts, keratinocytes, macrophages, endothelium cells, Langerhans dendritic cells, neurons, microglial cells, myocytes and

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Effects of the IL6 -174G>C promoter polymorphism and IL-6 serum levels on the progression of cutaneous malignant melanoma

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Received September 3, 2019; Accepted March 26, 2020

DOI: 10.3892/ol.2020.11740

Abstract. Cutaneous malignant melanoma (CMM) is one of the most immunogenic types of cancer, with a 6-fold higher rate of spontaneous regression than any other malignancy. In addition to responsiveness to different immunotherapies, the immunogenicity of CMM highlights the important role of the host immune system in the response to CMM. The present study aimed to explore the role of two functional promoter polymorphisms [*IL6* -174G>C (rs1800785) and *TNFA* -308G>A (rs1800629)] in the regulation of the genes encoding the pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor-α, specifically in patients with CMM. A total of 76 patients with CMM and 200 control subjects were genotyped using PCR-restriction fragment length polymorphism. The genotype frequencies for both single nucleotide polymorphisms (SNPs) did not differ significantly between the patients and controls (P=0.358 and P=0.810 for IL6 and TNFA, respectively). However, compared with carriers of C-allele genotypes (CG+CC), patients with the *IL6* -174GG genotype exhibited more advanced melanoma (Clark scale ≥3; P=0.037) and shorter survival times, particularly those who worked outdoors (in conditions with increased sunlight exposure; P=0.016). Furthermore, the serum IL-6 levels of patients with CMM were significantly higher than those of the control subjects, which were associated with unfavorable blood and serum characteristics and tumor progression (development of new distant metastases; P=0.004), and with a shorter overall survival time (P=0.042). Using a Cox proportional hazard model, the *IL6* -174GG genotype was found to be an independent prognostic factor for reduced survival time (P=0.030), together with sex (being male; P=0.004) and occupations with higher exposure to sunlight (P=0.047). In conclusion, the results of the present study indicated that the promoter polymorphisms *IL6* -174G>C and *TNFA* -308G>A are not predisposing factors for CMM. However, the *IL6* -174G>C SNP and IL-6 serum concentrations are likely to influence the progression of the disease, and the GG genotype and higher IL-6 serum levels may indicate shorter survival.

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Key words: melanoma, cytokines, polymorphism, interleukin-6, tumor necrosis factor-α

Introduction

Cutaneous malignant melanoma (CMM) is the most life-threatening primary skin malignancy, with a high global incidence rate amongst the Caucasian population. In Bulgaria, >470 new cases of melanoma are diagnosed each year (1). Once diagnosed, CMM can remain latent for a long period of time or can rapidly metastasize. Following distant metastasis, patient prognosis is poor, with an average survival time of 6-8 months, with only 11% of patients surviving beyond 2 years (2-4).

Numerous studies have investigated the genetic factors involved in the development of sporadic melanoma, including genes involved in the regulation of skin pigmentation, the cell cycle, DNA repair, the oxidative stress defense system and the production of immune modulatory mediators (5-12). Previous evidence also suggested that patients with CMM mounted an efficient immune response towards the tumor leading in some cases to spontaneous regression, although in most cases these responses did not prevent tumor progression (13,14). The pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) are among the factors involved in this response (13,15). IL-6 is a major pro-inflammatory mediator produced by various cell types, including melanoma cells, which exerts different biological activities towards a variety of target cells (16,17). IL-6 is reportedly involved in the differentiation of myeloid-derived suppressor cells and the reinforcement of their suppressive function; it is also associated with increased production of immunosuppressive cytokines by tumor cells, and increased metastasis in melanoma (18,19). Furthermore, the expression of IL-6 has been shown to promote the progression of CMM. Elevated pre-treatment levels of serum IL-6 have been determined as an independent prognostic biomarker of

Глава 13
Някои лабораторни изследвания в пулмологията.

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Всички белодробни болести са асоциирани с възпалителен отговор, който може да бъде остър или хроничен, локален и/или системен и, в зависимост от патофизиологичните механизми на развитие на конкретната болест, се характеризира с различен комплекс от молекулни медиатори и клетъчни фактори, които могат да бъдат оценени. В тази връзка, наред с инструменталните образни и функционални тестове и анализи, за поставяне на по-точна диагноза и уточняване на прогнозата, в практиката се изследват и редица локални и системни цитологични или биохимични променливи. Някои от тях са много добре познати и рутинно се прилагат, други имат допълваща роля, а трети са нови, които все още не са навлезли широко в съвременната клинична практика в България (Табл. 1).

Табл. 1. Най-често изследвани променливи при заболявания на БД (Адаптирана по [1-3]).

Цитологични променливи	
Локални (храчки, БАЛ, биопсии)	НТ, МА, еозинофили, CD4+, и CD8+ Т-клетки
Системни (плазма и серум)	НТ, МА, еозинофили, CD4+, и CD8+ Т-клетки
Биохимични променливи	
Локални (храчки, БАЛ, биопсии)	
	CRP, фибриноген, IL-6, IL-8, MPO, TNFα,прокалцитонин, периостин
Системни (плазма и серум)	CRP, фибриноген, IL-6, IL-8, левкотриени, TNF-α
Издишан въздух	FeNO, CO

Алфа$_1$-антитрипсин и ААТ дефицит

Алфа$_1$-антитрипсиновият (ААТ) дефицит е наследствено заболяване, свързано с ранно развитие на ХОББ, ЕМ, бронхиектазии, черно-дробна цироза при деца и възрастни, и по-рядко на системен васкулит и неоплазии[4]. Тежък ААТ дефицит най-често се среща в популации от Кавказки тип с честота от 1:2000 до 1:5000. ААТ е 52 kDa едноверижен гликопротеин, изграден от 394 аминокиселини. Синтезира се главно в черния дроб и функционира като серпин (serpin) – инхибитор на серинови протеинази, осигурявайки основна защита на белодробната тъкан от действието на протеолитични ензими, като неутрофилната еластаза (NE) и протеиназа 3 (PR3)[5]. При тежък ААТ дефицит, анти-еластазната защита на БП спада до 15-20% от нормалните нива, пропорционално на намаляването на серумните нива[6].

ААТ се кодира от гена *SERPENTINA1*, изграден от 7 екзона и локализиран на дългото рамо на хромозома 14 (14q31-32.3). Досега са установени над 500 еднонуклеотидни полиморфизми (SNPs), унаследявани по автозомен кодоминантен механизъм. Традиционната номенклатура на протеиназните инхибитори (Pi) използва буквени съкращения за подчертаване скоростта на миграция на различните алелни варианти при електрофореза на гел. С буквата M се отбелязва най-често срещаният „нормален" алел, докато най-често срещаните варианти, които водят до дефицит, са S и Z. Те мигрират по-бавно. Фенотипът по отношение на протеиназните инхибитори (Pi) отразява типа на циркулиращия ААТ, идентифициран чрез електрофореза на серум, докато генотипирането се основава на ДНК анализи. Болшинството от хората са хомозиготни по нормалния M алел. Рядко, индивиди могат да унаследят тъй наречените „нулеви" алели, които не продуци-

5

Glutathione-S-Transferases in Development, Progression and Therapy of Colorectal Cancer

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1. Introduction

Etiologically, sporadic colorectal cancer (CRC) is a complex, multifactorial disease that is linked to both exogenic and endogenic factors. Accumulating evidence indicates that susceptibility to cancer in general, and to CRC in particular, is mediated by genetically determined differences in the effectiveness of detoxification of potential carcinogens and reactive oxygen species. The antioxidant enzymes and phase I and II biotransformation enzymes are important candidates for involvement in susceptibility to sporadic CRC, due to their ability to regulate the metabolism of a wide range of environmental exposures (Perera, 1997; Potter, 1999; McIlwain et al., 2006; Di Pietro et al., 2010). In addition to carcinogens and reactive oxygen species, the majority of anticancer drugs applied in the chemotherapy are also substrates and are biotransformed by xenobiotic-metabolizing enzymes, leading to their activation and/or detoxification (O'Brien &Tew, 1996; Eaton &Bammler, 1999; Townsend &Tew, 2003; Hayes et al., 2005; Michael &Doherty, 2005; Townsend et al., 2005). In this respect, great efforts have been focused to clarify the effects of genetic variations, expression and activity of xenobiotic-metabolizing enzymes in development, progression and therapy of cancers with different histological origin, including CRC (Ranganathan &Tew, 1991; Tew &Ronai, 1999; Welfare et al., 1999; Cotton et al., 2000; de Jong et al., 2002; Dogru-Abbasoglu et al., 2002; Stoehlmacher et al., 2002; Ates et al., 2005; Romero et al., 2006; Liao et al., 2007; Pistorius et al., 2007; Koutros et al., 2009; Di Pietro et al., 2010; Economopoulos & Sergentanis, 2010).