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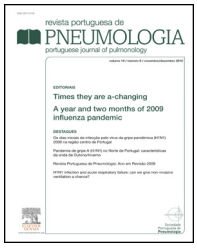

ORIGINAL ARTICLE

Caffeine consumption and exacerbations of chronic obstructive pulmonary disease: Retrospective study

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Abstract
Background: The modulation of adenosine receptors has been proposed as new therapeutic target for chronic obstructive pulmonary disease, but studies in humans were negative. Caffeine is widely consumed and acts by non-selective modulation of these receptors, allowing for a non-interventional evaluation of the purinergic effects on COPD. We evaluated the effects of chronic caffeine consumption on the risk for COPD exacerbations.
Methods: Retrospective study including patients with COPD. The total number of exacerbations during a three-year period and the mean daily caffeine consumption in the last twenty years were evaluated. A univariate and multiple regression analysis were performed for evaluation of the significant predictors of exacerbations.
Results: A total of 90 patients were included. Most were males (82.2%) and had a mean forced expiratory volume in the first second (FEV1) of 57.0 ± 17.1% predicted. The mean daily caffeine consumption was 149.7 ± 140.9 mg. There was no correlation between the mean caffeine consumption and exacerbations ($p > 0.05$).
Discussion: Our results suggest that caffeine has no significant effect on the frequency of COPD exacerbations. These conclusions are limited by the sample size and the retrospective nature of the study.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive, non-reversible airflow obstruction, leading to disability and premature death. Exacerbations are frequent episodes of increasing symptoms and inflammation, besides a major driver of morbidity and

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mortality from the disease. Most exacerbations are caused by bacterial/viral infection or exposure to pollutants. Importantly, some patients seem to be especially prone to exacerbations (frequent exacerbator phenotype), and each episode increases the risk for a new one. COPD usually develops as a late complication of cigarette smoking, with biomass and occupational exposure having smaller roles.[1] The disease is highly prevalent, and the associated morbidity and mortality are growing. The World Health Organization estimates that COPD will be the third leading cause of worldwide death in 2030.[2] Current treatments have no significant effects on its progression, and so new therapies are urgently needed.[3]

One potential new therapeutic target is the modulation of purinergic receptors, which have been shown to have potent anti-inflammatory and immunomodulatory effects.[4] However, despite promising results in animal models, the clinical use of purinergic modulators in COPD has not shown efficacy, probably due to differences in receptor types and distribution among species.[5]

Caffeine, the most widely consumed psychoactive substance exerts its effects by non-selective antagonism of adenosine receptors.[6] This allows for an estimation of the potential of adenosine receptor modulation on COPD patients, by studying the consequences of caffeine intake. Our objective was to evaluate the effects of chronic caffeine consumption on the risk of exacerbations of COPD patients.

Materials and methods

We performed a retrospective study, including patients with COPD under follow-up at the outpatient consult of the Unit of Pneumology of an Academic Hospital in Portugal. The inclusion criteria were a diagnosis of COPD according to international guidelines[1] and performance of at least one post-bronchodilator spirometry in the three previous years. The exclusion criteria were a diagnosis of another pulmonary or systemic inflammatory disease, asthma, pregnancy and non-consent. Patients were selected from the outpatient clinics database and contacted by telephone. After oral consent was given, a standardized questionnaire was applied. The purpose of the interview was the estimation of mean daily caffeine consumption in the last twenty years, and the number of exacerbation in the last three years. Patients were questioned about the mean daily consumption of the main dietary caffeine sources: espresso = 100 mg, instant coffee (cup) = 60 mg, decaffeinated coffee = 3 mg, tea (leaves, herbs or berries) = 30 mg, instant tea (cup) = 20 mg, cola-drinks (300 ml can or bottle) = 18 mg.[7] The average daily consumption of caffeine was calculated by multiplying the amount of caffeine content in each source by its mean daily consumption. An exacerbation was defined as a period of worsening symptoms leading to urgent medical evaluation. The subjects were also asked about their demography, habits and clinical history, including comorbidities. The questions about comorbidities focused on hypertension, stroke and peptic ulcer disease as the study investigators considered that these diseases could impact caffeine consumption. Patient's clinical files were reviewed for data on COPD diagnosis and lung function tests.

The statistical analysis was performed using the STATA software package version 13.1 (StataCorp, USA). The continuous variables were characterized using measures of central tendency (mean) and distribution (standard deviation), and the categorical variables were characterized using proportions. The group differences in quantitative variables were tested with Student's t test for independent variables or Wilcoxon rank-sum test, according to normality, as tested by Shapiro–Wilk. For more than two groups, ANOVA or Kruskal–Wallis was used. The correlations were tested using Pearson or Spearman coefficient, depending on normality. The relationships between categorical variables were tested using chi-square. For the analysis of the effect of caffeine consumption on the frequency of exacerbations, a multiple regression model was built using a step-down procedure. A p-value < 0.05 was considered statistically significant. The sample size was also calculated using STATA. For a power of 0.8 and α-value of 0.05, a sample of 85 individuals was necessary to test for a correlation of 0.3 between caffeine consumption and exacerbation rate.

Results

An initial sample of 100 patients was contacted but 10 were excluded due to an alternative diagnosis (8) or concomitant systemic inflammatory disease (2). Our final sample included 90 patients. The demographical and clinical characteristics of the study population are described in Table 1. Patients were predominantly male, with a mean age of 73.0 ± 10.6 years. The majority were smokers (15.6%) or former smokers (46.7%), with a mean of 56.0 ± 33.2 pack years of tobacco lifetime exposure. Former smokers had quit 17.5 ± 12.0 years before this study. Concerning COPD severity, most patients had GOLD spirometric stage 2 disease, with a mean forced expiratory volume in the first second (FEV1) of $57.8 \pm 17.1\%$ predicted. A significant proportion (36.7%) were on long term oxygen therapy (LTOT). Comorbidities were common, including hypertension in 72.2% and stroke in 11.1% of patients. When comparing genders, we found differences in smoking history (31.3% of smokers or former smokers in females vs 68.9% in males, $p < 0.01$, chi square), and oxygen therapy (68.8% in females vs 29.7% in males, $p < 0.01$, chi-square). There were no other significant differences between genders in demographical or clinical features.

The patient's frequency of exacerbations can be seen in Table 2. Patients reported a mean of 2.33 ± 3.70 exacerbations during the three years of the study, with 0.74 ± 1.57 leading to admission. There was no significant correlation between age and the number of exacerbations ($p = 0.72$, Spearman). There was also no difference regarding gender ($p = 0.90$, Mann–Whitney), history of smoking ($p = 0.20$, Mann–Whitney) hypertension ($p = 0.59$, Mann–Whitney) and stroke ($p = 0.31$, Mann–Whitney). There was a trend for higher number of exacerbations for patients under LTOT ($p = 0.077$, Mann–Whitney), and an unexpected lower number of exacerbations in patients reporting a diagnosis of peptic ulcer disease (PUD) (mean of 0.95 ± 1.67 vs 2.73 ± 4.03, $p < 0.05$, Mann–Whitney). A