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[EFFECT OF CAFFEINE CONSUMPTION ON THE EVOLUTION OF SARCOIDOSIS]

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Effect of caffeine consumption on the evolution of sarcoidosis

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Abbreviation List

ATS – American Thoracic Society

ERS – European Respiratory Society

WASOG – World Association of Sarcoidosis and other Granulomatous Disorders

HUC – Hospitais da Universidade de Coimbra (Coimbra's University Hospital)

FVC – Forced vital capacity

FEV1 - Forced expiratory volume in 1 second

Abstract

Sarcoidosis is a systemic granulomatous inflammatory disease of unknown etiology that primarily affects the lung tissue. One commonly used therapeutic is the use of methotrexate, an immunomodulating drug, acting through adenosine-mediated modulation. This led us to gauge the impact of caffeine, an antagonist of adenosine receptors of the evolution of sarcoidosis. In a retrospective study involving 46 patients diagnosed with sarcoidosis and followed at the University Hospital of Coimbra, we ranked the evolution of sarcoidosis through the evolution of pulmonary efficiency (evaluated as the forced vital capacity) and CT scan staging and applied a questionnaire to evaluate their caffeine consumption over the past 20 years. It was found that the consumption of caffeine failed to modify the evolution of the disease, and this was not hindered either by smoking habits or the introduction of drug therapy. Interestingly, these patients consumed higher amounts of caffeine before diagnosis when compared to a group of healthy individuals. Overall, these results suggest that caffeine consumption fails to affect the evolution of sarcoidosis, albeit the higher consumption of caffeine might by future sarcoidosis patients hints at a possible self-medication strategy that should deserve further investigation.

Key words:

caffeine, sarcoidosis, coffee, adenosine, respiratory function, inflammation, lung

Resumo

A sarcoidose é uma doença inflamatória e granulomatosa sistémica de etiologia desconhecida que afecta sobretudo o tecido pulmonar. Um fármaco frequentemente utilizado é o metotrexato, um imuno-modulador, que actua através da modulação dos receptores de adenosina. Estas informações levam-nos a avaliar o impacto de cafeína, um antagonista dos receptores de adenosina, da evolução da sarcoidose.

Realizámos um estudo retrospectivo, envolvendo 46 pacientes com diagnóstico de sarcoidose seguidos nos Hospitais da Universidade de Coimbra, que avaliou a evolução clínica da sarcoidose e a relacionou com o consumo de cafeína por parte destes. Foram utilizados como parâmetros indicadores da evolução da doença os danos na função pulmonar (avaliados através da variação da capacidade vital forçada) e o estadio da doença obtido por tomografia computadorizada do tórax, e aplicou-se um questionário para avaliar o consumo de cafeína ao longo dos últimos 20 anos. Verificou-se que o consumo de cafeína falhou em modificar a evolução da doença, e que esta não foi alterada pelos hábitos tabágicos ou pela introdução de terapia farmacológica. Curiosamente, estes pacientes consumiam maiores quantidades de cafeína antes do diagnóstico, quando comparados com um grupo de indivíduos saudáveis. Globalmente, estes resultados sugerem que o consumo de cafeína não afecta a evolução da sarcoidose, embora um maior consumo de cafeína por pacientes possa indiciar que se trate de uma estratégia de auto-medicação possível e que deve merecer uma investigação mais aprofundada.

Introduction

Sarcoidosis is an inflammatory systemic granulomatous disease that preferably affects the lungs; it can affect both genders and all ages, but is more frequent between the ages of 20 and 39 years (Iannuzzi et all. 2007).

The cause of the disorder is still unknown, but environmental, genetic and immunologic factors are potentially responsible. Accordingly, sarcoidosis is characterized by a Th1-like immune-inflammatory response involving activated macrophages and $CD4^+$ T lymphocytes (ATS/ERS/WASOG, 1999).

Sarcoidosis is frequently asymptomatic, and in many cases diagnosed by routine chest X-ray; in other cases nonspecific constitutional symptoms, dyspnea, dry cough, mucus or chest pain occur (Iannuzzi et all. 2007).

Therapy for sarcoidosis, when required, is based on oral corticosteroids, but their frequent long-term side-effects (Baughman et al., 2008) often force using immunomodulating drugs such as methotrexate. Methotrexate is the most frequently used immunomodulating drug, which works trough an indirect modulation of adenosine receptors (Baughman et al., 2008).

Adenosine is a purinergic nucleoside, with is a major STOP signal of the immune-inflammatory system trough the activation of adenosine A_{2A} receptors (Ohta e Sitkovsky, 2009). The importance of this immuno-modulation system is best illustrated by the current targeting of A_{2A} receptors to manage conditions as diverse as asthma, arthritis, organ transplant, cancer or sepsis (Ohta e Sitkovsky, 2009). Notably, this adenosine modulation system is also targeted by the mostly wide consumed stimulating substance in the world, caffeine (Fredholm et al., 1999).

Epidemiological studies have shown that chronic consumption of moderate doses of caffeine is associated with an improvement in lung function (Geraets et al., 2010a) and a symptomatic improvement in lung diseases such as asthma (Schwartz e Weiss, 1992) or pulmonary emphysema (Sturani et al., 1986). The observation that caffeine is a powerful driver of immune-inflammatory responses (Ohta e Sitkovsky, 2009), particularly in the lungs (Nettleton et al., 2009), raises the possibility of caffeine consumption can have an impact on the evolution of sarcoidosis.

Thus, the purpose of this study is to evaluate the impact of caffeine consumption on the clinical evolution of sarcoidosis. This was investigated in a retrospective cohort study including 46 patients with sarcoidosis, and 49 controls, where their average consumption of caffeine during the 20 years before the study was evaluated and compared to the rating of their clinical evolution, gauged using respiratory function and radiological data.

Methods

Enrolled cases and controls:

This study enrolled 46 individuals of both genders, over 18 years old, smokers and non-smokers, under different therapies, who attended the pulmonology out-patient consult at HUC, and have been diagnosed with sarcoidosis, according to ATS/ERS/WASOG criteria. The age, gender, date of diagnosis and recommended therapeutics of these patients is summarized in Table I. We also evaluated 49 healthy individuals of both genders, over 18 years old, with an age average similar to that of the patients' cohort.

Questionnaire to estimate the consumption of caffeine:

The questionnaire used was previously validated for the estimation of caffeine consumption in a Portuguese population (Maia and de Mendonca, 2002); here, it was applied to estimate the consumption of beverages containing caffeine (*Espresso* coffee, instant coffee, decaffeinated coffee, tea infusion, instantaneous tea, and cola-drinks) in cups or bottles per day in the last 20 years (1990-2009) while also registering socio-demographic characteristics such as gender, age, job, ethnic background, marital status, educational level and dates of first symptoms and diagnosis. This questionnaire was completed through an interview, which was conducted face-to-face after the consult, or when this was not possible, by telephone, by two distinct researchers. All interviews to controls were performed face-to-face by one of the two researchers.

Caffeine intake was calculated by adding the estimated caffeine contents for the different consumed beverages. According to Barone and Roberts (1996), the following standardized values were used for caffeine contained in the sources – *espresso* coffee: 100 mg, instantaneous coffee: 60 mg, decaffeinated coffee: 3 mg; tea infusion: 30 mg, instantaneous tea: 20 mg, cola-drinks: 18 mg. The annual average of caffeine intake (mg/year) was estimating by calculating the cumulative intake of caffeine from all sources.

The time interval used to estimate this annual average intake of caffeine depended on the age of the patients, since we only considered the intake of caffeine at ages above 18 years old, based on the social standard habits of coffee consumption in the Portuguese population.

Clinical evaluation:

The clinical data were gathered through the analysis of the clinical files stored at the pulmonology outpatient consult of the University Hospitals of Coimbra. This consisted in the staging of patients using either the chest X-ray (stage 0: normal; stage I: bilateral hilar lymphadenopathy (BHL); stage II: BHL plus pulmonary infiltrations; stage III: pulmonary infiltrations (without BHL); stage IV: pulmonary fibrosis) and/or the chest CT using the Scading criteria as well (Rajesh Sharma et al., 2004), an analysis carried out by a qualified imagiologist. Additionally, we ranked for each patient the evolution of lung function (FVC and FEV1/FVC ratio – FEV1%), which is routinely performed using *Masterscreen PFT* or *Masterlab body*, from Jaëger (calibrated daily). All tests were performed by certified respiratory technicians, and predicted values were calculated using referential equations published by Quanjer et al., (1993).

The FVC values and the CT stage variation were determined for each interval between consultations for each patient, which can vary between 5 and 332 months. This data was collected by two distinct researchers for all consultations between the time of diagnosis and the last observation.

Statistical analysis:

The statistical analysis was performed using *PASW Statistics* software, version 18. The sample characterization was done by calculating measures of location (arithmetic mean and median) and measures of spread (standard deviation, interquartil range) for quantitative variables and by determining absolute and relative frequencies for qualitative variables.

Age and sex prevalence comparison between the study group and the controls was done using student *t* test for independent samples and chi-square test, respectively. Caffeine consumption between the two groups was compared using Mann-Whitney test. Comparison of caffeine consumption pre- and post-diagnosis was performed using Wilcoxon Test. For non-smokers and smokers (previous or actual), correlation of caffeine consumption with mean FVC variation per year and with CT stage variation was performed by calculating Pearson and Spearman correlation coefficient, respectively. The same procedure was done considering the groups composed by individuals submitted to pharmacologic therapeutics and those who were not.

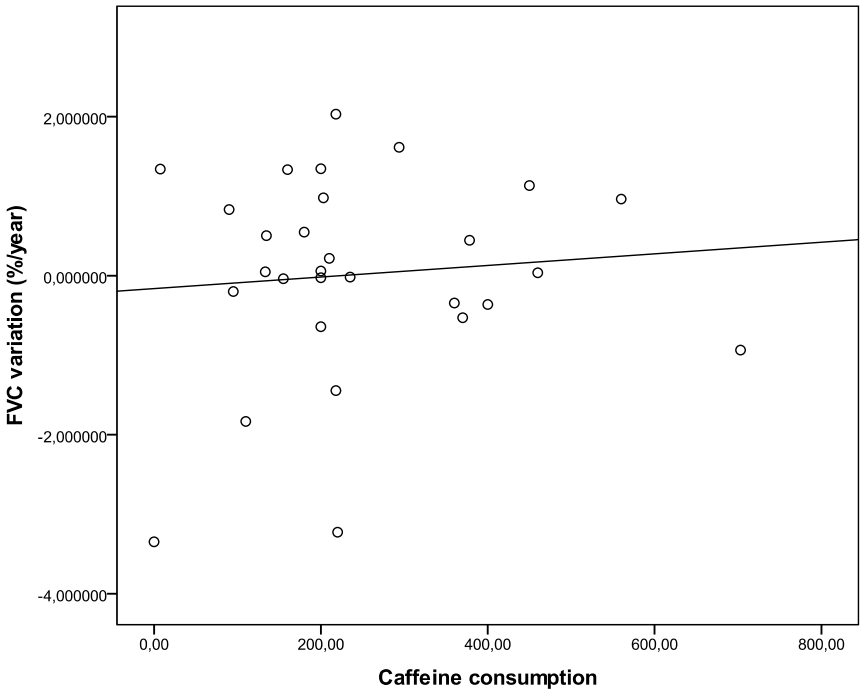
All analysis were carried out establishing a significance at 95% confidence, unless otherwise explicitly defined.

Results

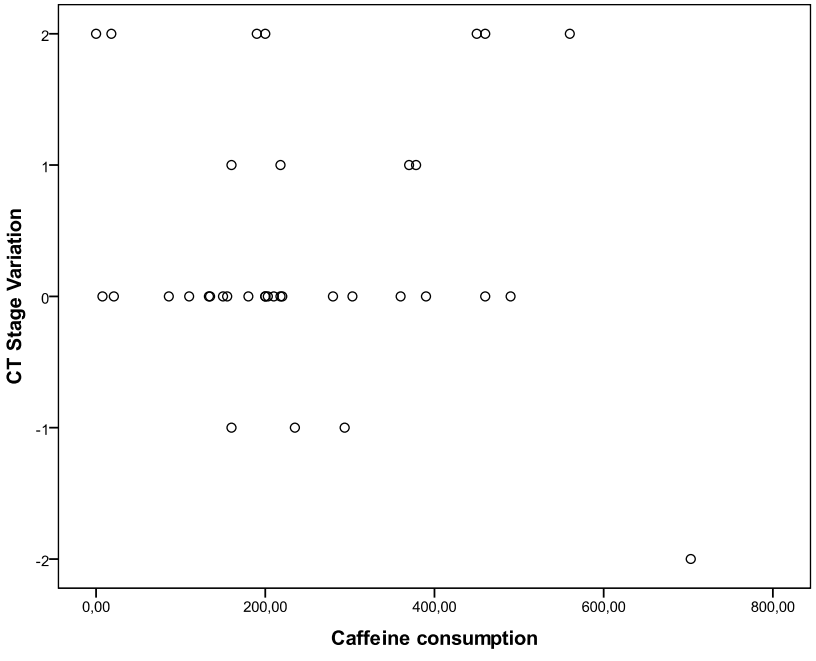
Impact of caffeine on the clinical evolution of sarcoidosis:

We first assessed the impact of caffeine consumption on the variation of pulmonary efficiency over time, gauged by the variation of FVC values. This variation of FVC values per year could only be determined for 29 patients since several patients only had one FVC determination in their clinical records. In this set of the cohort (see Table I), we found a mean variation of FVC of 0.017±1.278 %/year. As shown in Figure 1A, there was no significant correlation caffeine consumption and FVC variation (Pearson coefficient, R= 0.091, p= 0.639).

We next investigated the impact of caffeine consumption on the staging of the disease based on CT scan analysis. This analysis was carried out using 36 patients, who were subjected to more than one CT scan. In this set of the cohort (see Table I), the median variation of CT stage was 0 with an inter-quartile range of 1. As shown in Figure 1B, there was no significant correlation between caffeine consumption and the evolution of CT staging (Spearman coefficient, R= -0.015, R^2= -0.0002, p= 0.931).



A



B

Figure 1 - Lack of effect of caffeine consumption on the clinical evolution of sarcoidosis, evaluated either through the yearly evolution of the pulmonary function (gauged by measuring the variation of forced vital capacity, FVC, between visits) or the variation of CT scan staging between visits. All the individual data points for the 29 patients with more than one FVC determination (A) and for the 36 patients with more than one CT scan (B).

Possible influence of drug treatment or smoking habits on the impact of caffeine on disease evolution:

We next tested if two potentially major interfering variables could hinder this absence of effect of caffeine consumption on the evolution of sarcoidosis. We first investigated if the introduction of a pharmacological management could be responsible for this lack of effect of caffeine: For this purpose, we segmented the initial cohort into two sub-groups, namely treated and non-treated patients and investigated the impact of caffeine consumption in each of these groups in terms of variation of FVC and of CT staging.

The mean variation of FVC for treated patients (n=15) was 0.203±1.139 %/year, and for non-treated patients (n=14) was 0.060 ± 1.361 %/year. As shown in Figures 2A and B, caffeine consumption failed to significantly modify FVC variation in either treated patients (R= -0.110, p= 0.697) or in non-treated patients (R= 0.274, p= 0.343). The median variation of CT stage for treated (n=20) and non-treated (n=16) patients was 0 with an inter-quartile range of 1. Again, as shown in Figures 2C and 2D, caffeine consumption failed to significantly modify the evolution of CT staging in either treated patients (R= 0.072, p= 0.763) or non-treated patients (R= -0.083, p= 0.759).

We next investigated if smoking habits might interfere with the ability of caffeine to affect the evolution of sarcoidosis. To allow sufficient statistical power to apply a chi-square analysis, we grouped current and ex-smokers. The mean variation of FVC for non-smokers (n=22) was -0.137 ± 1.186 %/year, and it was 0.845 ± 0.985 %/year for smokers (n=7). As shown in Figure 3A, caffeine consumption did not affect FVC evolution in non-smoking patients (R= 0.231, p= 0.300); however, as shown in Figure 3B, caffeine seemed to increase the loss of FVC in smoking patients (R= -0.752, p= 0.051). However, this apparent effect of caffeine on the evolution of sarcoidosis in the sub-group of smoking patient was not confirmed when evaluating the CT staging. The median variation of CT

stage for non-smokers (n=27) is 0 with an inter-quartile range of 1 and it was 0 with an inter-quartile range of 2 for smokers (n=9). As shown in Figure 3D and E, caffeine was devoid of effects on the evolution of CT stating in either non-smoking patients (R= -0.180, p= 0.369) or smoking patients (R= 0.075, p= 0.849)

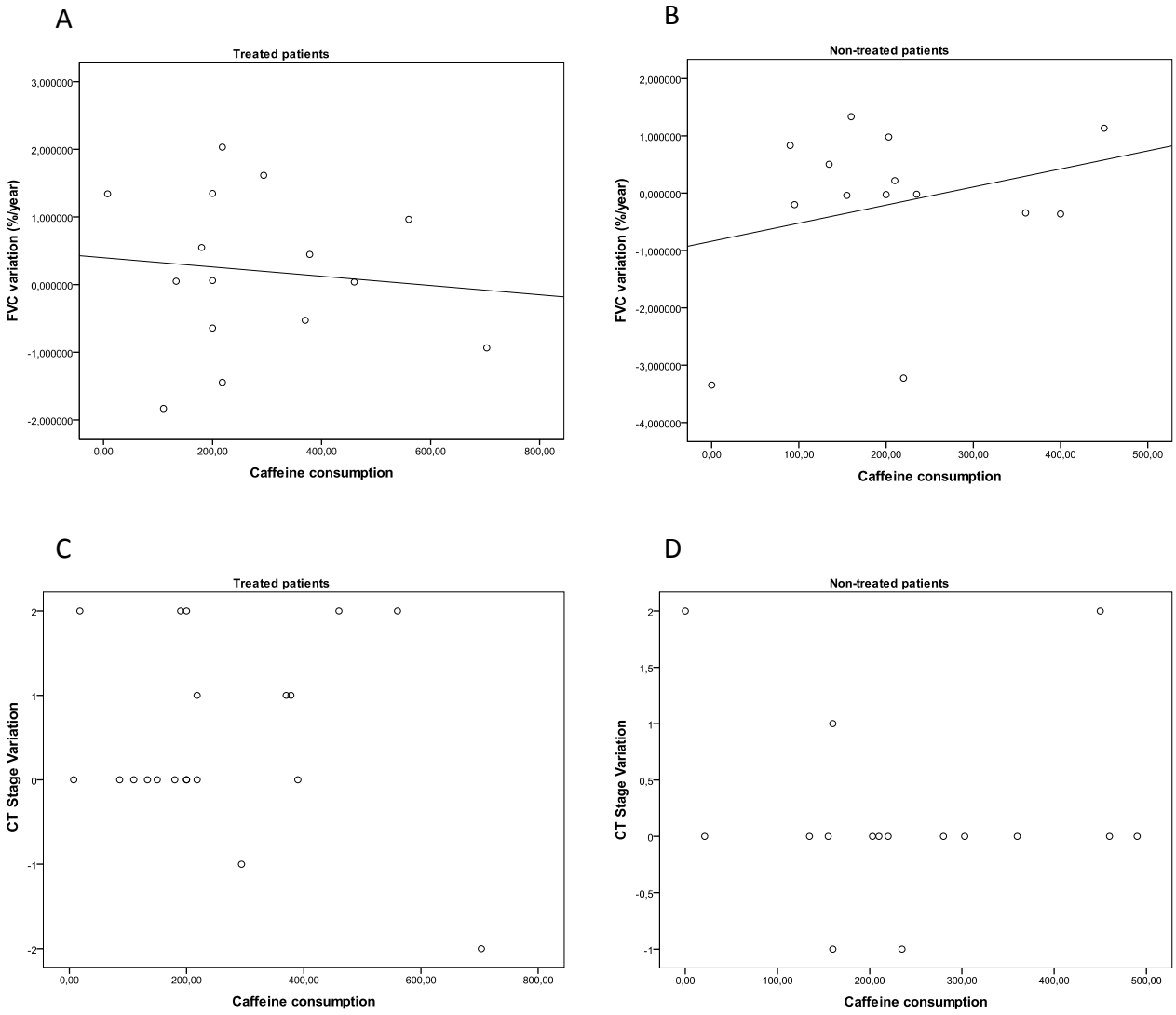


Figure 2 - The introduction of a drug therapy does not affect the lack of effect of caffeine consumption on the clinical evolution of sarcoidosis. In fact, the consumption of caffeine failed to modify the yearly evolution of the pulmonary function (gauged by measuring the variation of forced vital capacity, FVC, between visits) either in treated (n= 15, A) or in non-treated patients (n=14, B); likewise, the consumption of caffeine also failed to modify the yearly variation of CT scan staging between visits either in treated (n=20, C) or in non-treated patients (n=16, D).

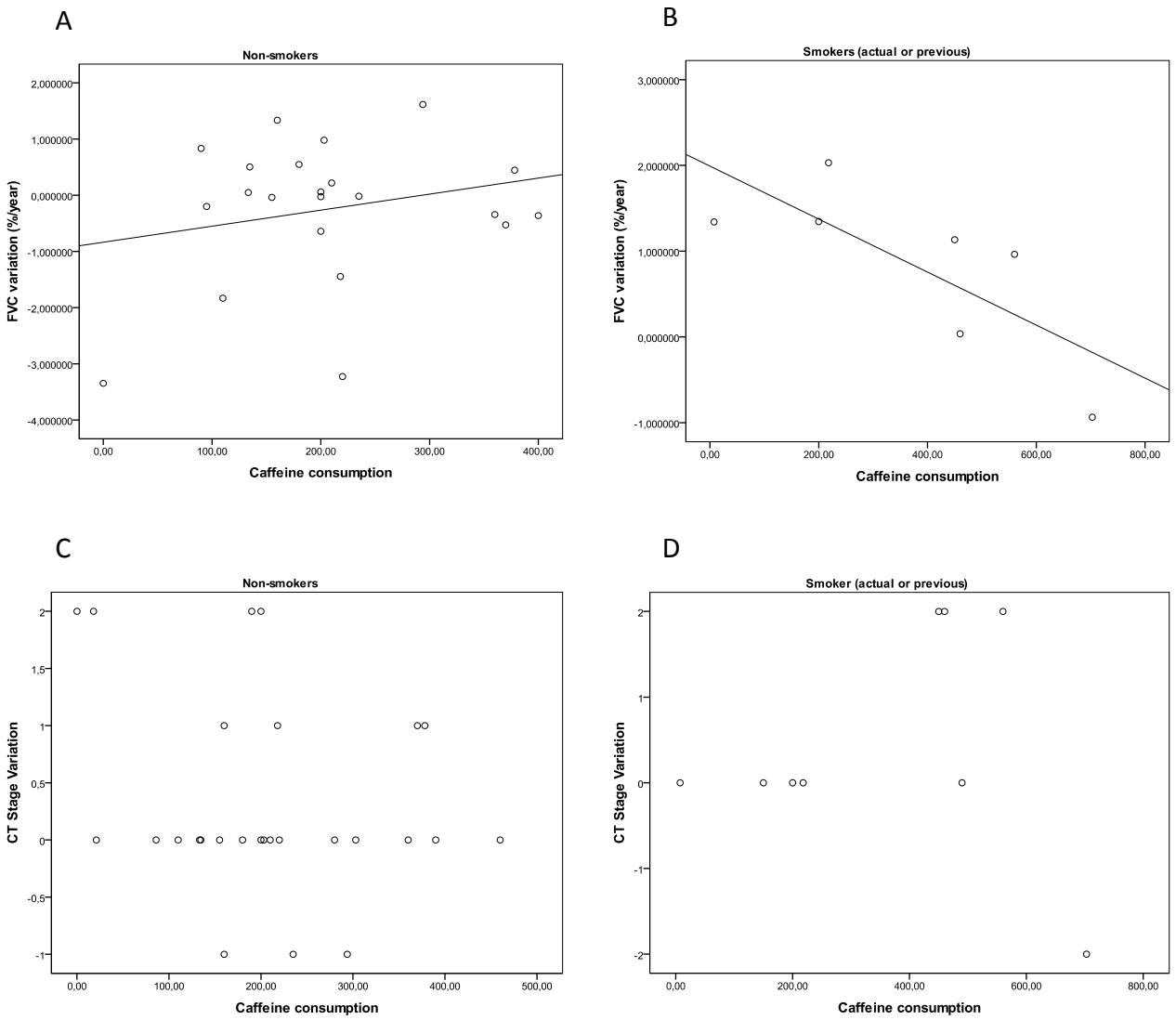


Figure 3 - Smoking habits do not seem to affect the lack of effect of caffeine consumption on the clinical evolution of sarcoidosis. The consumption of caffeine failed to modify the yearly evolution of the pulmonary function (gauged by measuring the variation of forced vital capacity, FVC, between visits) in non-smoking (n= 22, A) but seemed to enhance the deterioration of pulmonary function in smoking patients (n=7, B); however, the consumption of caffeine failed to modify the yearly variation of CT scan staging between visits either in non-smoking (n=27, C) or in smoking patients (n=9x, D).

Comparison of caffeine consumption in patients and healthy individuals:

We next evaluated if the consumption of caffeine in the 20 years previous to the diagnosis of sarcoidosis was different in the cohort of patients analysed comparing to a group of healthy individuals. The group of healthy individuals, all Caucasians as the patients' group, had an average age (42.1±14.3 years, n= 49) slightly lower (p= 0.041; *t* test for independent samples) than that of patients (48.2±14.2 years, n=46), whereas gender distribution was not significantly (p= 0.155; chi-square test) between the 2 groups (42% and 56% males in healthy individuals and patients, respectively). It was found that the average consumption of caffeine was significantly higher (p= 0.040; Mann-Whitney test) in patients (236.3±156.3 mg) compared to healthy individuals (203.9±127.5 mg).

The last question we addressed was whether patients modified their habits of caffeine consumption upon diagnosis of sarcoidosis. The comparison between the average consumption of caffeine before and after diagnostic shows that there was a tendency for a decrease of caffeine consumption (-17.8±132.9 mg, p= 0.638, n=46) after diagnosis.

Discussion and Conclusions

The main conclusion of this study is that the consumption of caffeine fails to affect the evolution of sarcoidosis. We further confirmed that neither the life style of the patients (namely their smoking habits) nor the introduction of a therapeutic strategy to manage the symptoms was responsible for this lack of effect of caffeine. This global conclusion is rather surprising in view of the proposed primary involvement of immune-inflammatory processes in the progression of sarcoidosis. As a matter of fact, in several other conditions where the abnormal functioning of the immune-inflammatory system plays a role, it has been shown that the consumption of caffeine affects the evolution of these diseases, this has been observed in conditions such as arthritis (Choi e Curhan, 2010) or diabetes (van Dam e Hu, 2005). In particular, the consumption of caffeine is associated with a modification of inflammatory parameters in healthy individuals, as well as, individuals suffering from endothelial pathologies such as diabetes, cardiovascular dysfunction or alcoholic liver injury (Hamer et al., 2006; Kempf e Martin, 2010; Lopez-Garcia et al., 2006; Lv et al., 2010). Caffeine consumption also affects the incidence or evolution of different carcinomas, especially the ones displaying a stronger immunologic component (Ohta e Sitkovsky, 2011). This is generally in agreement with the ability of adenosine A_{2A} receptors, the likely target of non-toxic doses of caffeine (Fredholm et al., 1999), to control immune and inflammatory responses (Ohta e Sitkovsky, 2009). Furthermore, caffeine has also been reported to affect lung function and lung pathology (Chapman e Mickleborough, 2009; Nettleton et al., 2009; Welsh et al., 2010) and to modulate inflammatory responses in the lung (Geraets et al., 2010). Thus, the presently lack of evident effects of caffeine consumption on the evolution of sarcoidosis clearly favour the view that this pathology is associated with specific imbalances in the response of particular lymphocytic populations (Facco et al., 2011) rather than the overt hyper-reactivity of the main components of the

immune-inflammatory system in the evolution of sarcoidosis (Iannuzzi e Fontana, 2011; Katchar et al., 2003).

When attempting to detail the possible influence of two major factors that could interfere with the impact of caffeine consumption on the evolution of sarcoidosis, namely smoking and drug therapy, we further confirmed the lack of effect of caffeine in any of these sub-groups of patients. In fact, the utilized drug strategies are all known to affect the adenosine modulation system and hence potentially affect the actions of caffeine: corticosteroids interfere with the adenosine modulation system (Nordeen et al., 1995; Scaccianoce et al., 1989) and methotrexate acts through adenosine receptors (Cronstein et al., 1994). Furthermore, it has been documented that the effects of caffeine are dependent on nicotine consumption (Nettleton et al., 2009), in accordance with the molecular interaction between adenosine and nicotinic receptors (Duarte-Araújo et al., 2004). Regarding the smoking factor as a confounding parameter, it was observed that FVC but not CT scan staging was aggravated by caffeine in smoking patients, but the reduced number of cases fitting these criteria (n=7) precludes any conclusive statement at present. Thus, this attempted segmentation further re-enforces our main conclusion that caffeine consumption fails to affect the evolution of sarcoidosis.

The data gathered in this study provides one additional conclusion showing that the in individuals who latter developed sarcoidosis consumed a greater amount of caffeine than control healthy individuals. This could suggest two alternative scenarios: 1) that caffeine might be considered a precipitating factor for the establishment of sarcoidosis, or 2) that caffeine consumption might be a self administered drug retarding the onset of symptoms. The latest hypothesis is difficult to conceive since no healthy patient is able to anticipate the latter occurrence of a pathology; in contrast, the former hypothesis is attractive in view of the recent demonstrations that the consumption of caffeine is related to polymorphisms

of the adenosine A_{2A} receptor gene (Cornelis et al., 2007), which is associated with the incidence of different pathologies (Gomes et al., 2011). However, if confirmed in subsequent prospective studies, this observation would imply that the mechanisms of initiation and progression of sarcoidosis might be different, in view of their different susceptibility to caffeine.

Finally, it is interesting to note that the comparison of caffeine consumption before and after diagnosis of sarcoidosis show that the patients modify their pattern of caffeine consumption. This might well result from the widespread recommendation by doctors for patients to abstain from caffeine consumption and from the general perception that caffeine consumption might be harmful. In fact, this study argues against such a rationale since we presently observed that caffeine consumption was devoid of effects on the evolution of sarcoidosis. Certainly, the recommendations should be the opposite, after all, the consumption of caffeine seems to be inversely associated with several disorders, namely with age-related disorders such as diabetes (van Dam e Hu, 2005), cardiovascular diseases (Lopez-Garcia et al., 2009) or brain disorders (Cunha e Agostinho, 2010).

In conclusion, the present study suggests that caffeine consumption might not affect the evolution of sarcoidosis and indicate that individuals who will develop sarcoidosis seem to consume greater amounts of caffeine that healthy controls. It should be noted that the strength of these conclusions is limited by the size of the cohort of patients analyzed and by the design of the study as a retrospective collection of information. It is hoped that future prospective studies carried out in a larger population of patients suffering from this pathology may confirm the presently proposed conclusions.

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Supplementary Data

Table I – List of cases with information on gender, age, diagnosis date, therapeutics, caffeine consumption in the last 20 years (mg/year), FVC variation and Thorax TC scan modification. Follow up begins with diagnosis and continues up to today. The therapeutics includes three kinds of drugs: corticosteroids (prednisolona, deflazacort), azathioprine and infliximab. For FVC variation the negative values represent loss of FVC, while the negative values on Chest TC variation represents a downstaging.

Cases	Gender	Age	Diagnosis Date	Therapeutics	Caffeine consumption variation	FVC Variation	Chest TC variation
C1	Male	36	17-12-2009	costicosteroids + azathioprine	293.7895	1.614465	-1
C2	Female	33	25-11-2009	0	303		0
C3	Female	66	22-03-2009	deflazacort	150		0
C4	Female	64	30-01-2008	0	220	-3.22672	0
C5	Female	58	02-12-2005	0	90	0.832682	
C6	Male	53	28-03-2007	prednisolone	560	0.963708	2
C7	Female	35	15-05-2000	prednisolone	133.3333	0.04807	0
C8	Male	27	17-12-2008	prednisolone	200	1.345455	0
C9	Female	26	24-11-2008	deflazacort	241		
C10	Female	59	31-08-2007	prednisolone	7,5	1.340822	0
C11	Male	37	21-09-2007	0	21		0
C12	Female	64	22-07-1993	prednisolone	180	0.547769	0
C13	Female	72	29-07-2005	0	155	-0.03876	0
C14	Male	52	10-11-2000	0	210	0.218183	0
C15	Male	61	28-01-2008	corticosteroids	460	0.036918	2
C16	Female	38	18-12-2003	0	390		

C17	Female	49	17-11-2005	0	235	-0.01821	-1
C18	Male	42	28-09-2009	corticosteroids	218	2.031146	0
C19	Male	35	10-07-2008	0	360	-0.34438	0
C20	Male	50	20-06-2007	prednisolone	218	-1.44597	1
C21	Male	46	05-05-2003	prednisolone	200	-0.64213	2
C22	Female	52	16-03-2007	prednisolone	703	-0.93596	-2
C23	Male	43	17-02-2009	deflazacort	18		2
C24	Male	54	20-09-1993	prednisolone	390		0
C25	Female	27	16-10-2008	0	90		
C26	Male	47	08-07-2008	prednisolone	378.2	0.445223	1
C27	Male	27	16-02-2005	corticosteroids	86		0
C28	Female	35	13-03-2009	0	298.5556		
C29	Male	45	20-12-2007	prednisolone	200	0.058727	0
C30	Male	34	14-03-2007	0	134.6667	0.503278	0
C31	Female	50	05-07-2005	prednisolone	370	-0.52842	1
C32	Male	35	16-10-2008	0	0		2
C33	Female	26	16-10-2008	0	157.5		
C34	Female	36	10-09-2007	0	0	-3.34780	
C35	Male	57	03-03-2006	0	200	-0.02548	
C36	Female	71	09-03-2006	predisolone	110	-1.83296	0
C37	Male	77	10-09-2007	azathioprine + infliximab	190		2
C38	Male	50	04-10-2005	0	450	1.133382	2
C39	Male	48	03-10-2008	0	203	0.979546	0
C40	Male	45	03-02-2010	0	460		0
C41	Male	64	23-03-2009	0	280		0
C42	Male	70	20-07-2010	0	490		0

C43	Male	45	27-04-2009	0	400	-0.36288	
C44	Female	41	15-01-2009	0	160	1.334146	-1
C45	Male	80	18-09-2002	0	95	-0.19981	
C46	Female	53	11-04-2008	0	160		1

CENTRO DE PNEUMOLOGIA

Faculdade de Medicina da Universidade de Coimbra

Questionário de avaliação de consumo de **cafeína**

Este questionário destina-se a estudar uma possível relação entre o consumo de cafeína e a evolução da sarcoidose pulmonar.

Os dados nele contidos só servirão para estudo, pelo que garantimos o seu anonimato.

Por favor tente lembrar-se e responda de um modo preciso.

Agradeço a sua ajuda ao responder a este questionário!

Data: _____/_____/_____ Avaliador: _____

Nome _____ Nº processo: _____

Sexo: Masculino ☐ Feminino ☐ Data de nascimento: ____ / ____ / ____

Profissão: _____ Contacto telefónico: _____

Estado civil: Solteiro ☐ Casado ☐ Divorciado ☐ Separado ☐ Viúvo ☐ outro ☐

Raça: Branca ☐ Africana ☐ Asiática ☐ outra ☐

Grau de escolaridade: (assinalar com uma X)

1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	+4

Ensino básico Secundário Ensino superior

Data dos primeiros sintomas? ____ / ____ / ____ Data do diagnóstico ____ / ____ / ____

1- Tanto quanto se lembra, qual foi o seu consumo de bebidas com **cafeína,** nos respectivos anos:

Bebida	**Quantidade**	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**
Café expresso	chávenas de café / dia											
Café instantâneo (inclui o "nescafé" misturado no leite)	chávenas de café / dia											
Descafeinado	chávenas de café / dia											
Chá (folhas, ervas, bagas)	chávenas de chá / dia											
Chá instantâneo	chávenas de chá / dia											
Bebida tipo "coca-cola" (Pepsicola, Spur-cola, etc)	lata ou garrafa 300ml/ dia											

Bebida	**Quantidade**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Café expresso	chávenas de café / dia											
Café instantâneo (inclui o "nescafé" misturado no leite)	chávenas de café / dia											
Descafeinado	chávenas de café / dia											
Chá (folhas, ervas, bagas)	chávenas de chá / dia											
Chá instantâneo	chávenas de chá / dia											
Bebida tipo "coca-cola" (Pepsicola, Spur-cola, etc)	lata ou garrafa 300ml/ dia											

Preencheu este questionário: -sem ajuda ☐ -com ajuda ☐ _____

Tem algum comentário ou sugestão a fazer: _____