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Corticosteroids and hip fracture risk in elderly respiratory patients: EPIC-Greece cohort

This work was supported by the Hellenic Health Foundation.

Abstract

Introduction: In an ageing population the prevalence of osteoporosis and chronic respiratory diseases is expected to increase in the near future. Interestingly, several forms of corticosteroids, drugs implicated in osteoporosis pathogenesis, are prescribed to respiratory patients without taking into consideration their age and risk for osteoporotic fractures. The aim of this study was to investigate the risk for hip fracture of the elder individuals who are taking corticosteroids for respiratory disease, including inhalers.

Material and methods: Data on incident hip fractures were collected through the active follow-up for all individuals participating in the Greek segment of the European Prospective Investigation into Cancer and Nutrition (EPIC-Greece) study who were 60 years or older at recruitment and reported "a doctor's diagnosis" of respiratory disease. Socio-demographic, life-style, health status data and use of corticosteroids were recorded from the baseline and follow-up questionnaires. Cox regression models were applied to estimate hazard ratios (HRs) adjusting for relevant confounders.

Results: We observed an increase in hip fracture risk with corticosteroid intake overall (HR: 1.68, 95% CI: 0.85–3.34). Increased risk persisted when we restricted our analysis to participants taking any form of corticosteroids for obstructive lung disease (HR: 1.40, 95% CI: 0.64–3.06) and to those using only inhalers (HR: 1.58, 95% CI: 0.71–3.50). However, these positive associations did not reach the nominal level of significance probably due to the small number of participants with hip fractures during follow-up.

Conclusion: Hip fracture risk should be taken into consideration when recommending corticosteroids to the elder respiratory patients, including inhalers.

Key words: elderly, EPIC-Greece, corticosteroids, hip fracture, respiratory disease

Adv Respir Med 2017; 85: 22–27

Introduction

Older age is a well established risk factor for fractures. Among them hip fracture is a serious cause of disability and mortality in the elderly populations [1, 2]. Certain drugs, especially corticosteroids have been implicated to osteoporotic fractures' pathogenesis [3]. Respiratory patients very often receive several forms of corticosteroids (orally, injected or inhalants) either continuously or intermittently and thus, are at high risk for osteoporotic fractures [4]. The current evidence is less clear on the impact of inhaled corticosteroids (ICSs) currently used by patients having obstructive lung diseases [5]. According to a meta-analysis the overall prevalence of osteoporosis in chronic obstructive pulmonary disease (COPD) is 35% [6]. However, osteoporosis in this

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DOI: 10.5603/ARM.2017.0005
Received: 2.11.2016

ISSN 2451–4934

population is poorly identified and undertreated due to lack of specific guidelines. Needless to say that even more limited are the data concerning elderly populations.

Since the proportion of the elderly in the population is growing and COPD is also expected to rise and be one of the main causes of death by 2020 [7] the incidence of fractures is expected to significantly increase in the future. In an ageing population to keep older active for as long as possible it is necessary to recognize risk factors related to frailty, determine their distribution and implement prevention or optimize treatment.

In the present study, conducted in the context of the Greek segment of the European Prospective Investigation into Cancer and Nutrition (EPIC-Greece) study, we investigate the risk for hip fracture of elder individuals who are taking corticosteroids for a respiratory disease.

Material and methods

Study design-subjects

The study population consisted of all individuals participating in the EPIC-Greece study who were 60 years or older at recruitment and reported "a doctor's diagnosis" of respiratory disease. Participants who developed respiratory disease during follow-up were also included in the study.

EPIC is a prospective study conducted in 23 research centers across 10 European countries aiming to determine the incidence of and mortality from cancer and other diseases in relation to several individual characteristics, biologic, dietary, lifestyle and environmental factors [8–11]. In Greece, a total of 28,572 (men and women) apparently healthy volunteers aged 20-86 years were recruited from all regions of the country during 1994–1999. Among them 9,863 were aged ≥ 60 years. All procedures were in line with the Helsinki declaration for human rights, all volunteers signed informed consent forms, and the study protocol was approved by ethical committees at the International Agency for Research on Cancer and at the National and Kapodistrian University of Athens, School of Medicine. Sociodemographic, dietary, lifestyle and health data including "a doctor's diagnosed" disease, history of smoking and physical activity were obtained at enrollment by pre-coded questionnaires administered to each participant by specially trained interviewers. Anthropometry measurements were also undertaken by using standardized procedures [12]. During the study period, participants' vital status was ascertained by active follow up and information from mortality registries.

In the present study participants were selected based on age and self-reporting of "a doctor's diagnosis" of respiratory disease (ICD-10-CM diagnosis codes J00-J99). Individuals using inhalers (short or long acting β2 adrenergic and/or anticholinergics and/or corticosteroids) without ever having reported in the questionnaires "a doctor's diagnosis" of respiratory disease were also included as having "possible obstructive pulmonary disease". Finally, among participants those reporting chronic obstructive pulmonary disease (J44), asthma (J45) and emphysema (J43) were identified in order to perform additional subgroup analyses.

Hip fractures

Data on incident hip fractures were collected through active follow-up using telephone interviews or mailed questionnaires, eliciting self-reported information. In a validation study conducted in Greece, 79% of self reported cases of incident hip fractures were medically confirmed [13]. If there was more than one hip fracture recorded for the same individual, only the first one was used in the analysis.

Corticosteroids use

Information on systemic use of plain corticosteroids (H02A, ATC classification system) as well as use of inhalants corticosteroid (R03AB) or corticosteroids in combination with adrenergics (R03AK) was recorded from the baseline and follow-up questionnaires.

Body mass index and physical activity

Body mass index (BMI) was derived as the ratio of weight in kilograms divided by the square of height in meters.

The protocol we used to estimate physical activity for each participant has been described in detail in previous publications [14–15].

Analyses

In our analyses, to estimate hazard ratios (HRs) for hip fracture incidence, Cox regression was used adjusting for age, sex, educational level, BMI, physical activity and smoking status. For the participants with respiratory disease at baseline, the survival time was calculated from the date of enrollment at the study till the date of death (for those who died during the follow-up) or till the date of the last follow-up (for those who were alive at that time) or till the date of a hip fracture event (for those who faced a hip fracture event during the follow-up). For the participants that

developed a respiratory disease for the first time during follow-up, the date of entry for them in our analysis was assumed to be the date respiratory disease was first diagnosed. Subjects with missing values in variables included in the applied models were excluded from the analysis.

All analyses were carried out using the Stata Statistical Software, release 11 (StataCorp. 2009, StataCorp LP).

Results

A total of 2,487 elderly participants reporting "a doctor's diagnosis" of respiratory disease was identified. During a median follow-up of 10.9 years and a total contribution of 24,587 person-years, a total of 61 incident cases of hip fractures (51 women and 10 men) were recorded. Age, BMI, physical activity and educational status were similar between participants having a hip fracture and those who did not have (Table 1).

Out of all the above participants 2.5% had at least one hip fracture whilst this percentage increased to 2.9% when we included only those reporting having obstructive lung disease. About 10% of all study participants reported use of corticosteroids, mainly inhalants (77.2%), and 3.8% of them (overall) presented a hip fracture (5.9% and 3.4% under systemic use or use of inhalants respectively) (Table 1).

Corticosteroid intake increased hip fracture risk in all elderly participants reporting respiratory disease (HR: 1.68, 95% CI: 0.85–3.34) as well as to those with obstructive lung disease (HR: 1.40, 95% CI: 0.64–3.06). Moreover, increase in risk persisted when we restricted the analyses only to inhalant corticosteroids (HR: 1.58, 95% CI: 0.71–3.50). However, in all cases the associations did not reach the nominal level of significance probably due to the small number of participants with hip fractures during the follow-up (Table 2). Furthermore, this small number of incident fractures did not allow us to perform further subgroup analyses to estimate the risk of hip fracture for each one of the obstructive respiratory diseases (COPD, asthma or emphysema) separately.

Discussion

In this study performed in the context of EPIC-Greece study we observed an increase in hip fracture risk with corticosteroid intake (inhalants included) in elderly participants with chronic respiratory disease. The increase in risk remained after restricting the analyses only to the elderly with obstructive lung disease. However, the above mentioned increase did not reach the nominal level of significance mainly due to the small number of participants with hip fractures during the follow-up.

So far, to the best of our knowledge, studies relating risk of hip fractures in elder respiratory patients are lacking. Among these patients, those suffering from chronic obstructive lung disease mainly asthma or COPD often receive several forms of corticosteroids, drugs known to be implicated in the pathogenesis of osteoporosis and fractures [3, 4]. The development of osteoporosis is a major concern with oral corticosteroids [16]. However, previous studies examining the impact of ICSs on bone mineral density (BMD) of patients with asthma provide conflicting results. Some of them have found significant BMD changes whilst in others ICS administration was not associated with BMD changes in asthmatics [17, 18]. Similarly, mixed are the results from studies examining hip fracture risk in COPD patients and indicate that the effect may be dose dependent [19–21].

In the treatment of moderate or severe asthma corticosteroids are considered to be the mainstay (www.gina.org). However, the balance between risk and benefit concerning potential long term adverse events is not so clear for mild asthmatics, while there is lack of studies focusing on the elderly. In a study concerning patients with mild asthma but younger than 60 years, Tattersfield and coworkers report significant changes in bone density which were thought not to be clinically important in participants who use relatively low doses of ICS [18]. Another important issue that should also be considered in elderly patients are co-morbidities such as cardiovascular disease or left heart failure that may present with symptoms mimicking asthma leading thus to asthma overdiagnosis and consequently overtreatment with several forms of corticosteroids.

Chronic obstructive pulmonary disease is a major cause of morbidity and mortality worldwide [22]. In Greece the prevalence of COPD among smokers is 8.4% [23]. Overtreatment of COPD mainly with corticosteroids is an international phenomenon occurring also in Greece and is more pronounced in early stage and stable disease [24–26]. It is estimated that 38.8% and 51.8% GOLD Groups A and B, respectively, use corticosteroids although these patients do not meet the recommendation criteria [27]. Furthermore, screening for and treating osteoporosis is not clinicians' priority in this group of patients probably reflecting

Table 1. Characteristics of the elderly participants with respiratory disease in the EPIC-Greece study and distribution of corticosteroid use among them by hip fracture

	All	Hip fractures	
	(n = 2,487)	No (n = 2,426)	Yes (n = 61)
Age (years), mean (SD)	68.0 (5.2)	68.0 (5.1)	69.8 (5.0)
BMI (kg/m^2), mean (SD)	29.8 (4.8)	29.8 (4.8)	29.0 (5.2)
Physical Activity*, mean (SD)	33.6 (4.7)	33.6 (4.8)	33.5 (3.5)
Education, n (%)			
Elementary	2,145 (86)	2,091 (86)	54 (89)
High School-Lycee	235 (10)	230 (10)	5 (8)
University	107 (4)	105 (4)	2 (3)
Sex, n (%)			
Male	1,006 (40)	996 (41)	10 (16)
Female	1,481 (60)	1,430 (59)	51 (84)
Smoking status, n (%)			
Never	1,599 (64)	1,551 (64)	48 (79)
Former	567 (23)	559 (23)	8 (13)
Current	321 (13)	316 (13)	5 (8)
Respiratory disease, n (%)	2,487 (100)	2,426 (97.5)	61 (2.5)
COPD (J44)	52 (100)	48 (92.3)	4 (7.7)
Bronchial asthma (J45)	772 (100)	754 (97.7)	18 (2.3)
Pulmonary emphysema (J43)	127 (100)	121 (95.3)	6 (4.7)
Possible obstructive pulmonary disease**	53 (100)	52 (98.1)	1 (1.9)
Other	1483 (100)	1451 (97.8)	32 (2.2)
Corticosteroid use, n (%)	263 (100)	253 (96.2)	10 (3.8)
Systemic use, plain, n (%)	51 (100)	48 (94.1)	3 (5.9)
Inhalants, n (%)	203 (100)	196 (96.6)	7 (3.4)
Corticosteroids in combination with adrenergics, n (%)	30 (100)	28 (93.3)	2 (6.7)
Glucocorticoids, n (%)	173 (100)	168 (97.1)	5 (2.9)
Not specified form, n (%)	9 (100)	9 (100)	0 (0)

*metabolic equivalent task (MET)-hours/day; **participants using inhalants (short or long acting β2 adrenergic and/or anticholinergics and/or corticosteroids) without ever having reported in the questionnaires "a doctor's diagnosis" of respiratory disease

a wrong perception that inhaled corticosteroids are not "so bad" as systemic [28]. Thus, studies relating corticosteroids to fractures are important in order to persuade clinicians not to overtreat elderly patients.

The present study is nested in a large, well--established cohort that is the EPIC-Greece cohort. The EPIC study recruited subjects using standardized protocols and questionnaires. The study design substantially reduces the possibility of selection bias. A main limitation of our study is the small number of participants with hip fractures during follow-up that did not allow us to reveal significant associations. However, we believe that the consistent increase we observed in hip fracture risk with corticosteroid intake, inhalants included, in all sub-analyses we performed (all participants, only participants with obstructive lung disease, only participants using corticosteroid inhalants) suggests possible association.

Conclusion

Given the severe consequences of a hip fracture in the frail population of the elderly patients further studies are needed to determine the risk- benefit ratio of prescribing a medication of uncertain benefit such as corticosteroids to those suffering from chronic respiratory disease, COPD included. Moreover, specific guidelines

Table 2. Effect of corticosteroid use on hip fracture risk in respiratory patients compared to non-users (adjusting for age, sex, BMI, physical activity, educational level and smoking status)

	Hip fracture		
	Hazard ratio	95% CI	p
Corticosteroid intake (any form)			
Any respiratory disease	1.68	0.85–3.34	0.138
Obstructive lung disease*	1.40	0.64–3.06	0.406
Corticosteroid intake (inhalants- R03AK, R03AK06, R03AK07, R03BA)			
Any respiratory disease	1.58	0.71–3.50	0.260
Obstructive lung disease*	1.29	0.54–3.10	0.570

*COPD (J44), bronchial asthma (J45), pulmonary emphysema (J43) and participants using inhalants (short or long acting β2 adrenergic and/or anticholinergics and/ /or corticosteroids) without ever having reported in the questionnaires "a doctor's diagnosis" of respiratory disease

should be implemented for screening and treating osteoporosis in this population.

Conflict of interest

The authors declare no conflict interest.

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