Original Article

Hypertension and Asthma: A Comorbid Relationship

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What is already known about this topic? A number of prior epidemiologic studies have suggested that asthmatic subjects are more likely to manifest arterial hypertension than nonasthmatic subjects.

What does this article add to our knowledge? Using a case-control design, comorbid hypertension was found to be associated with established measures of adult asthma severity as reflected by the usage of short-acting β-agonist canister dispensing greater than 6, history of emergency department visits or hospitalizations, and corticosteroid dispensing. Angiotensin converting enzyme (ACE) inhibitor use was associated with a significantly increased risk for all 3 measures of asthma severity.

How does this study impact current management guidelines? Physicians treating these 2 common conditions should be aware of this association, which may have broader implications for systemic diseases involving endothelial and smooth muscle cellular differentiation, regulation, and remodeling.

BACKGROUND: An increased prevalence of hypertension has been described in adult asthmatic patients. However, there is no information regarding the interaction of hypertension as a comorbidity with asthma severity.
OBJECTIVE: The objective of this study was to investigate whether a concomitant diagnosis of hypertension had any impact on markers of asthma severity in adult asthmatic patients.
METHODS: A total of 117,922 asthmatic subjects 18 years or older were identified in the Kaiser Permanente database. Case-control studies were conducted with cases defined by short-acting β-agonist canister dispensing greater than 6 (SABA > 6), history of emergency department visits or hospitalizations (EDHO), and corticosteroid dispensings (CCS), respectively. Controls were matched by age and sex. Univariate and multivariate conditional logistic regression was applied to estimate the odds ratios (OR) and 95% confidence intervals (CI) for SABA > 6, EDHO, and CCS associated with the diagnosis of hypertension.
RESULTS: Hypertension was associated with an increased odds of SABA > 6 (OR 1.19, CI 1.13-1.26, n = 15,855 cases and 76,060 controls), EDHO (OR 1.11, CI 1.03-1.19, n = 9,307 cases and 46,535 controls), and CCS (OR 1.15, CI 1.10-1.19, n = 53,690 cases and 53,690 controls) after adjusting for potential confounders.
CONCLUSIONS: Asthmatic subjects with comorbid hypertension display evidence of enhanced of asthma morbidity. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Asthma; Hypertension; Smooth Muscle; Severity*

Both asthma and arterial hypertension are common diseases, and are frequently encountered together. A number of prior epidemiologic studies have suggested that asthmatic subjects are more likely to manifest arterial hypertension than nonasthmatic subjects.[1-6] A relationship between hypertension and asthma could potentially be explained by shared disease mechanisms. In each disease, vascular remodeling and endothelial abnormalities have been cited along with abnormal contraction and proliferation of smooth muscle cells.[7-11] Considering the epidemiologic association and potential pathophysiologic interplay, we felt it would be of interest to further explore the interaction between asthma and hypertension.

Potential relationships between these diseases have not been well studied. Asthmatic patients with comorbid conditions are more likely to report active asthma symptoms than asthmatic patients without a comorbid condition.[2] Whether hypertension impacts the severity of asthma, however, is not known. To address this question, we conducted case-control studies to examine whether a comorbidity of hypertension is associated with measures of disease severity in patients with physician-diagnosed asthma using administrative data in a large integrated health care maintenance organization.

METHODS

Study subjects

Kaiser Permanente Southern California (KPSC) is an integrated health care maintenance organization that has 3.8 million members. The membership constitutes approximately 15% of the region's

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Abbreviations used
ACE- Angiotensin converting enzyme
BMI- Body mass index
CCS- Oral corticosteroid dispensing
CI- Confidence intervals
DM- Diabetes mellitus
EDHO- History of emergency department visits or hospitalizations
GERD- Gastroesophageal reflux disease
HLD- Hyperlipidemia
MV- Multivariate
OR- Odds ratio
SABA>6- Short-actinβ-agonist canister dispensing > 6 in a 12-month period
UV- Univariate

population and is representative of the general population in terms of demographic and socioeconomic status.[12] The study utilized the administrative data from the KPSC's Research Data Warehouse. Study participants were selected from 117,922 members of KPSC, aged 18 or greater, who were identified with a physician diagnosis of asthma (ICD-9 code 493.xx) and with continuous Health Plan enrollment and drug benefits at Kaiser Permanente from 2004 through 2007. The study was approved by the KPSC Institutional Review Board.

Study design

Cross-sectional study. A cross-sectional design was applied to examine the relationship between a diagnosis of hypertension and asthma severity in the entire population of 117,922 asthmatic subjects, defined as asthma patients 18 years or older who met membership and drug benefit criteria between 2004 and 2007. Hypertension was identified by ICD-9 coding (401.xx). Asthma severity was defined by 3 different validated measures[13-15] during the 2004-2007 timeframe: (1) short-acting bronchodilator β-agonist (SABA) dispensing of greater than 6 canisters in a 12-month period (SABA > 6); (2) a history of visits to the emergency department (ED) for asthma exacerbations or hospitalizations for asthma exacerbations (EDHO); and (3) oral corticosteroid dispensing on encounters where asthma was coded as a diagnosis (CCS). All 3 outcome measures were coded and expressed as dichotomous (yes/no) variables.

Case-control study. To further explore the relationship between hypertension and asthma severity, case-control analyses were then performed, using cases defined by the same 3 measures of asthma severity (SABA > 6, EDHO, and CCS, respectively). The index date was determined as the date of the seventh SABA usage during the first qualified 12-month window in the study period or the date of the first hospitalization, ED visit, or CCS dispensing during the study period. For each analysis, controls were matched by age and sex using the index dates established above with the greedy method. The SABA > 6 and EDHO measures used 1 case to 5 control matching, whereas the CCS measure used 1 case to 1 control matching. Hypertension was identified by ICD-9 coding (401.xx).

Statistical analysis

All analyses were performed with SAS software (SAS Institute, Inc., Cary, NC). Nominal statistical significance was set at $P < .05$ for all analyses. Univariate (UV) and multivariate (MV) (adjusted for statin use, diabetes, hyperlipidemia, hypertension, reflux, asthma controller therapy, Angiotensin converting enzyme (ACE) inhibitor, β-blocker, Charlson score, and body mass index [BMI]) odds ratios (OR) and 95% confidence intervals (CI) were calculated by conditional logistic regression. The greedy method utilized a macro called "%gmatch" developed by the Mayo Clinic (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros). The Charlson comorbidity index assesses standardized comorbid conditions, with higher scores predicting enhanced mortality or higher resource use.

RESULTS

Cross-sectional study

As shown in Table I, a significant association between hypertension and each of the 3 measures of asthma severity was found by UV analysis. Multivariable analysis adjusting for BMI, gastroesophageal reflux disease (GERD), diabetes mellitus (DM), statin use, ACE inhibitor, β-blocker, race, Charlson score, and hyperlipidemia (HLD) showed a similar association between hypertension and enhanced asthma severity.

Case-control studies

Of the 117,922 asthma patients, 15,855 subjects received SABA > 6 between 2005 and 2007. Using the greedy method to match the 15,855 cases to controls based on gender and age within 5 years, we found that 15,212 had 5 controls, 1 had 4 controls, 3 had 3 controls, and 639 had no matches. The analyses were conducted on the 15,212 cases compared with their 76,060 controls.

A total of 9,307 cases had EDHO between 2005 and 2007. Using the greedy method to match these 9,307 cases to controls based on gender and age within 5 years, we found that each case had 5 controls. All cases and 46,535 controls were included for statistical analyses.

A total of 56,268 patients received CCS between 2005 and 2007. Using the greedy method to match the 56,268 cases to controls based on gender and age within 5 years, we found that 53,690 had 1 control and 2578 had no matches. A total of 53,690 cases and 53,690 controls were included for statistical analyses.

Table II shows the prevalence of hypertension in these groups, whereas Table III shows the characteristics associated with the presence or absence of hypertension. Study subjects were predominantly female (59.8%-67.2%) and white (44.9%-46.6%) with a mean age of 53.3-54.9 years. History of GERD, DM, or HLD as well as use of statin, ACE inhibitors, or β-blockers was strongly associated with hypertension (Table III).

Hypertension was significantly associated with SABA > 6, EDHO, and CCS in both unadjusted and MV analyses (Table IV). In the fully adjusted models, hypertension was associated with an increased risk of SABA > 6 (OR 1.19, CI 1.13-1.26), EDHO (OR 1.11, CI 1.03-1.19), and CCS (OR 1.15, CI 1.10-1.19). Compared with whites, blacks demonstrated significantly higher OR of SABA > 6 (1.10 [1.04, 1.16]), EDHO (2.15 [2.02, 2.29]), and CCS (1.08 [1.04, 1.12]). In contrast, compared with whites, Hispanics had significantly reduced OR of SABA > 6 (0.75 [0.71, 0.78]) but significantly increased OR of EDHO (1.34 [1.27, 1.42]). Reflux was associated with significantly higher OR of SABA > 6 (1.13 [1.08, 1.17]), EDHO (1.25 [1.19, 1.31]), and CCS (1.42 [1.38,