

Serum Total IgE and Specific IgE to *Dermatophagoides pteronyssinus*, but not Eosinophil Cationic Protein, Are More Likely to be Elevated in Elderly Asthmatic Patients

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ABSTRACT

Serum IgE (total and five specific) and eosinophil cationic protein (ECP) levels were compared in elderly physician-diagnosed patients with asthma with non-asthmatic controls matched by age and gender to ascertain whether elevated levels are indicators of asthma in the elderly. All subjects and controls were non-smokers. The subjects were participants in the Florida Geriatric Research Program (FGRP), a longitudinal aging study that tracks the health status of people 65 years and older. Frozen sera from 33 randomly selected

asthmatic patients and 21 controls, none of whom had any other chronic respiratory disease, such as chronic obstructive pulmonary disease (COPD), all between the ages of 65 and 90, were assessed for total IgE; five specific IgE concentrations (for cat, ragweed, German cockroach, *Dermatophagoides pteronyssinus* (Dp) and live oak); and ECP levels using the Pharmacia Unicap™ System. The odds of an elderly asthmatic patient having a total IgE of >100 KU/L were higher than that for a non-asthmatic patient (odds ratio (OR) = 13.0; Mantel-Haenszel (MH) $p = 0.005$). The odds of elderly asthmatic patients having at least one positive serum specific IgE compared to elderly age-matched non-asthmatic patients were higher (OR = 21.2; MH $p = 0.001$). Among the five specific IgE concentrations, only IgE for Dp was higher in asthmatic than in non-asthmatic patients (OR = 13.00; MH $p = 0.005$). The ECP level was not significantly different between elderly asthmatic and non-asthmatic patients (asthmatic mean = 20.7 $\mu\text{g/L}$, SE = 0.48; control mean = 19.5 $\mu\text{g/L}$, SE = 0.76) (mean for younger adults 4.4 $\mu\text{g/L}$, Pharmacia Diagnostics). The serum of elderly asthmatic patients is more likely to have elevated total IgE and a positive specific IgE to Dp. ECP is elevated in elderly subjects but is not an indicator of asthma. (Allergy and Asthma Proc 25:321–325, 2004)

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Physicians who examine elderly patients with wheezing and shortness of breath frequently associate these symptoms with chronic obstructive pulmonary disease

(COPD), chronic bronchitis, or emphysema. If asthma is diagnosed in the elderly, it is frequently assumed to be intrinsic or non-allergic in etiology, a definition introduced by Rackemann in 1947, which differentiated intrinsic (non-allergic) from extrinsic (allergic) asthma.^{1,2} The few studies of elderly populations with asthma that have determined serum immunoglobulin (IgE) were summarized by Barbee with some studies showing that even in the elderly, the presence of asthma is correlated with IgE levels, but other studies have not confirmed such a relationship.² The largest study (2657 subjects) in a general population concluded that asthma is almost always associated with some type of IgE-related reaction, and therefore has an allergic basis.³ Elevated eosinophil cationic protein (ECP), a highly cytotoxic protein found in the eosinophil, has been associated with asthma exacerbations in children and younger adults,⁴⁻⁷ but there are no reports of ECP levels in the elderly. When ECP is found in serum and other body fluids it is a marker of eosinophil degranulation.⁸

Serum IgE (total and specific) and ECP levels were determined in elderly asthmatic patients, without other chronic respiratory diseases and who were non smokers, and compared with levels in age/gender matched non-smoking, non-asthmatic controls, to ascertain whether they are indicators of asthma in the elderly and to identify specific allergen sensitivities in elderly asthmatic patients.

METHODS

Subjects and Controls

The subjects and controls were participants in the Florida Geriatric Research Program (FGRP), a longitudinal aging study of subjects over age 65. The FGRP in Clearwater, FL has followed 7878 subjects longitudinally for 26 years. Sixty-three per cent are women, and all were over age 64 at entry. This study has always been open to all races; however, the majority of the subjects who chose to enroll are Caucasian. Since 1975, the Florida Geriatric Research Program (then known as the Dunedin Program) began gathering data by questionnaire and routine screening exams on cardiovascular disease and lifestyle activities of participants. The original objective of the program was to study normal aging, hypertension, and their relationship to cardiovascular disease and cardiovascular outcomes of geriatric patients. The Institutional Review Board of Morton Plant–Mease Hospitals and the University of South Florida approved the study and all subjects gave informed consent.

Respiratory Questionnaire

All subjects who visited the FGRP in 1997 were asked to complete a questionnaire that included questions about the diagnosis of chronic respiratory diseases. Fig. 1 summarizes the complete answers by 1329 subjects who were non-smokers and answered yes or no to the four questions: Has a physician told you that you have 1) asthma,

FGRP study population (total 1329 subjects)

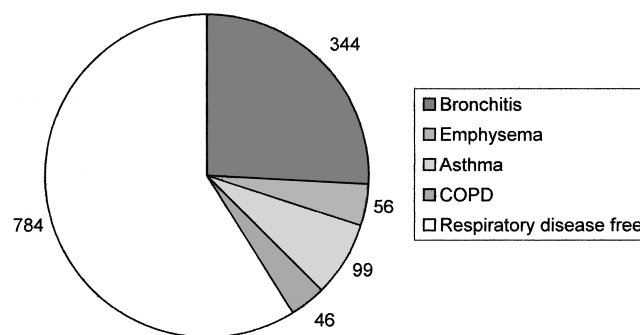


Figure 1. Distribution of chronic respiratory diseases among non-smokers by respiratory diagnosis in FGRP study population ($n = 1329$).

2) chronic bronchitis, 3) emphysema, or 4) chronic obstructive pulmonary disease (COPD).

Validation of Questionnaire

Of subjects who answered yes to having asthma, 28 had current telephone numbers, were at home, and agreed to be interviewed. They were interviewed by one of two investigators and asked to answer a secondary questionnaire. Two subjects did not recall being diagnosed as having asthma by a physician. The interviewers concluded the initial questionnaire was valid.

Exclusion and Selection Criteria

Thirty-three of the 99 asthmatic patients were selected by random digit assignment and all 99 had sera available. Then 33 age-, gender-matched non-asthmatic controls who answered no to all of the four chronic respiratory disease questions were identified and 21 had serum samples available. IgE and ECP levels were determined on frozen sera from the 33 randomly selected non-smoking, physician-diagnosed asthmatic patients and from 21 non-smoking, respiratory disease-free control subjects matched by age and gender.

Laboratory

Sera had been stored and maintained at -15°C until they were assessed for total IgE, five specific IgE concentrations (cat, ragweed, cockroach, *D. pteronyssinus* (Dp), and live oak) and ECP levels using the Pharmacia Unicap System (Uppsala, Sweden). Laboratory personnel were blinded as to whether the serum specimens were from the asthma or control groups.

Statistics

The strength of association between test results and asthmatic status was evaluated by calculating p -values for Spearman correlation coefficients and Mantel–Haenszel odds ratios.

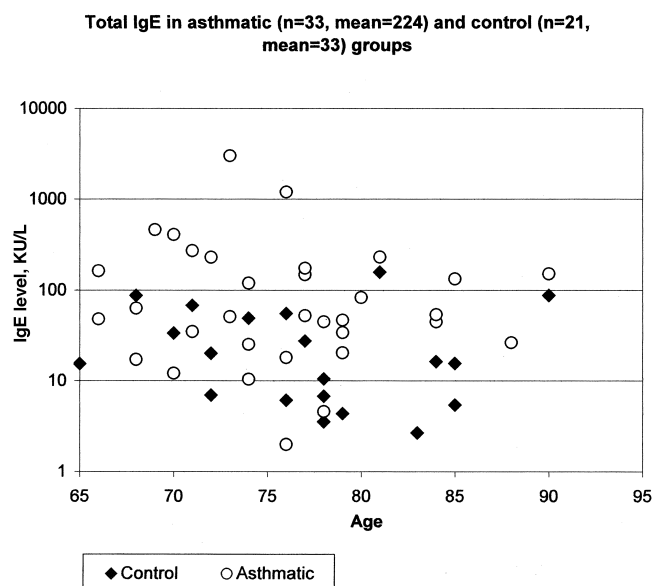


Figure 2. Total IgE in asthmatic ($n = 33$) and control ($n = 21$) group. Mean total IgE is elevated in elderly patients (mean = 224 KU/L, $p = 0.01$) but normal in controls (mean = 33 KU/L). Eleven asthmatic patients have total IgE levels >100 KU/L, whereas only one control subject has an IgE > 100 KU/L (odds ratio = 13.0 MH, $p = 0.005$). There is a trend for asthmatic patients to have lower total IgE levels with advancing age, whereas control subjects' mean total IgE levels remain nearly constant.

RESULTS

Mean total IgE is significantly elevated ($p = 0.01$) in elderly asthmatic patients (mean = 224.5 KU/L) compared to controls (mean = 33.9 KU/L). Eleven asth-

matic patients had total IgE levels >100 KU/L, while only one control subject had an IgE value >100 KU/L. In a previous study reported by Zetterström and Johansson a level of 100 KU/L was present in 78% of 252 atopic subjects with respiratory disease.⁹

The odds of elderly asthmatic patients having a total IgE of above 100 KU/L were higher than for non-asthmatic patients (OR = 13.0; MH $p = 0.005$). There is a trend for both asthmatics and controls to have lower total IgE levels with advancing age, but not of statistical significance (Fig 2).

Of the five specific IgE concentrations determined, only IgE for *Dp* was higher in asthmatic than in non-asthmatic patients (OR = 13.00; MH $p = 0.005$.) Although the odds ratio of ragweed was higher in asthmatic than in non-asthmatic patients (OR = 5.38 MH) it is not of statistical significance (Fisher exact: 1-tailed p -value = 0.099). The odds ratio of serum of elderly asthmatic patients having at least one positive specific IgE was 21.2 MH, $p = 0.001$. (Fig 3) Subjects were classified as atopic if they had one or more positive specific IgE test results (>0.35 KU_a/L) and total IgE levels were significantly higher in atopic than non-atopic subjects ($r = 0.53$, $p < 0.0001$).

There is no significant difference between older asthmatic ECP levels (mean = 20.7 μ g/L) and older control ECP levels (mean = 19.5 μ g/L) but mean levels are elevated in both asthmatics and controls in this study compared to healthy younger adults (mean 4.4 μ g/L). Although elevated compared to younger adults, ECP decreased significantly with increased age in elderly asthmatic and non-asthmatic groups ($p = 0.01$) (Fig 4).

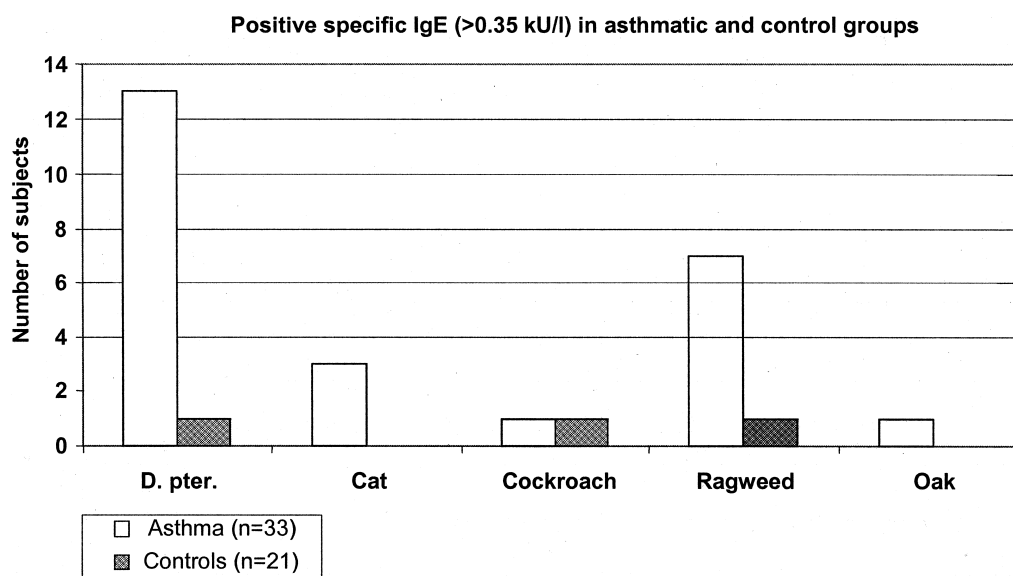


Figure 3. Positive specific IgE (>0.35 KU/L) in asthmatic and control groups. Seventeen subjects with asthma had at least one positive specific IgE test, whereas 13 had no positive tests (MH odds ratio = 21.2, $p = 0.001$). Only one subject in the control group had a positive specific IgE response. *D. pteronyssinus* was the most commonly positive allergen.

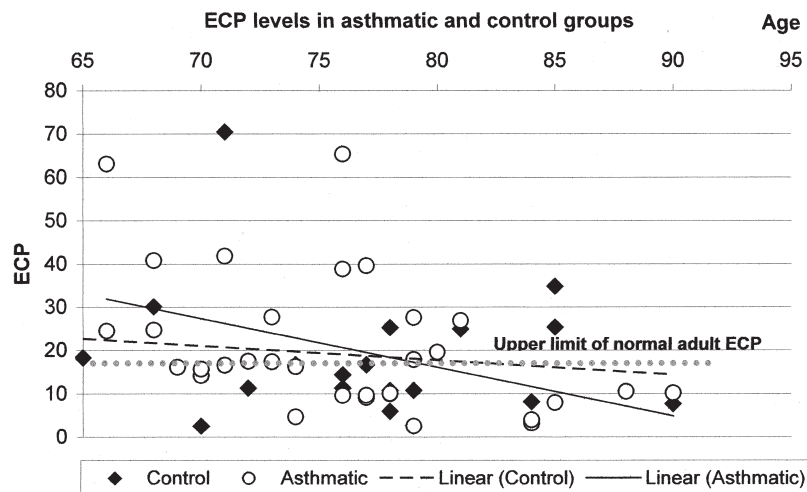


Figure 4. ECP levels in asthmatic and control groups. ECP is a marker of eosinophil activity, reported to be high in acute asthmatic patients. ECP decreased significantly for older subjects in both asthmatic and control groups ($p = 0.01$). There is no difference between older asthmatic patients (mean = 20.7 $\mu\text{g/L}$) and older controls (mean = 19.5 $\mu\text{g/L}$), but ECP levels are elevated compared to normal younger adults (mean 4.4 $\mu\text{g/L}$). The reference level for elevated ECP for adults age 18–54 is above 15 $\mu\text{g/L}$ (Pharmacia Unicap).

TABLE I

No Correlation among Age, Gender, Age at Asthma Diagnosis and Total IgE, ECP, or D_p

Age at Serum Draw	Gender Male = 1 Female = 2	Age at Asthma Diagnosis	Total IgE (KU/L)	ECP ($\mu\text{g/L}$)	D_p (KU _a /L)
66	2	42	48	63.1	<0.35
66	2	65	18	38.8	<0.35
68	2	63	17.1	24.7	<0.35
68	2	53	63.1	40.8	<0.35
69	2	13	34.8	41.8	8.42
70	2	14	408	15.7	1.09
70	2	4	12.1	14.2	<0.35
71	2	36	272	16.6	22.9
72	2	70	230	17.5	<0.35
73	2	6	3022	27.7	>100
73	1	15	462	16.1	0.38
74	1	64	10.4	4.67	<0.35
74	2	40	25.2	16.3	<0.35
74	2	78	148	9.64	4.56
76	2	unknown	<2.00	9.58	<0.35
76	1	67	1204	65.3	<0.35
77	2	unknown	163	24.5	<0.35
77	2	61	174	39.6	0.73
77	2	56	52.3	9.1	<0.35
78	2	15	4.59	10	<0.35
78	1	9	44.9	10.1	<0.35
79	2	18	46.6	2.58	4.32
79	2	unknown	20.3	17.9	<0.35
79	2	25	34	27.6	2.8
80	1	50	83.2	19.6	1.64
81	2	40	232	26.9	<0.35
84	2	80	53.8	4	<0.35
84	2	21	44.9	3.28	<0.35
85	2	75	133	7.97	8.36
88	1	20	26.4	10.5	3.55
90	2	87	151	10.2	<0.35

DISCUSSION

The findings of elevated total serum IgE and specific IgE to *Dp* in about half of the subjects with asthma appears to be independent of the age of onset and is only slightly lower with increasing age. There was no relationship between age of onset and positive specific IgE among the asthmatic patients (Table I).

An elevation of ECP levels in the elderly has not been previously reported and there is very little written about eosinophil activity in the elderly. Pharmacia Laboratories, the manufacturer of the Unicap system and the reagents, has no information about levels in the elderly (Personal communication with Stefan Ahlstedt, Pharmacia). Possible technical reasons for the elevated levels include hemolysis or delayed separation of the serum from the eosinophils. A temperature greater than 24°C while clotting and/or a delay between clotting and separation of more than 120 minutes may allow more eosinophils to release ECP.¹⁰ It is possible that the serum was not separated from the cells early enough to prevent eosinophil breakdown before freezing the serum. Future studies to confirm the finding of elevated IgE levels in the elderly and to determine age-specific reference values for healthy elderly subjects are needed. ECP is a potential valuable, simple test of eosinophil activation, useful in differentiating between allergic and non-allergic asthma.

Seventeen of 33 elderly asthmatic patients had a total IgE >100 KU/L, a positive specific IgE test to at least one allergen, or both. Thus about half of the elderly asthmatic patients had increased IgE activity. Only one of the 21 non-asthmatic subjects had positive specific IgEs to allergens (*Dp*, German cockroach, and ragweed) and another non-asthmatic subject had an IgE of 158 KU/L. The serum of elderly asthmatic patients is more likely to have elevated total IgE and specific IgE to *Dp*. Total and specific IgE to common allergens are good predictors of asthma in the elderly. The serum ECP level was not significantly different between elderly asthmatic patients and non-asthmatic patients (asthmatic mean = 20.7 µg/L, non-asthmatic mean = 19.5 µg/L; mean value for healthy younger adults = 4.4 µg/L, Pharmacia Diagnostics) and is not an indicator of asthma in the elderly, because ECP levels were higher in both the asthmatic and non-asthmatic elderly population compared to younger adults.

In a cohort of 45 elderly asthmatic patients enrolled in the Bellevue Hospital Asthma Clinic in New York City (NYC), cockroach sensitization was present in 47% and dust mite

sensitization in 18%. The asthmatic subjects in the FGRP are from a suburban Florida environment and 33% are sensitive to dust mites, with only one sensitive to cockroach. Mean IgE levels in the NYC cohort were 47 KU/L compared to 224 KU/L in the FGRP cohort. The subjects in the New York City study had more severe asthma, were also primarily women, but were more likely of minority racial/ethnic groups.¹¹

Therefore there are at least two phenotypes of elderly asthmatics, one with IgE activity and one without, confirming Rackeman's observation.

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