Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma

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Background: Limited data are available on levels of IgE in large cohorts of patients with severe or difficult-to-treat asthma.

Objective: To examine IgE levels and disease in patients from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study.

Methods: From January 2001 to October 2001, 4,923 patients were screened for inclusion in the study. Of these, 4,756 patients 6 years or older with severe or difficult-to-treat asthma were enrolled and completed a baseline study visit. Total serum IgE levels were measured at the baseline visit and are summarized by geometric means.

Results: The mean total IgE level of the population is 106.6 IU/mL (95% confidence interval, 101.5–112.0 IU/mL). Children (6–12 years old) and adolescents (13–17 years old) have higher mean IgE levels than adults (≥18 years old) ($P < .001$). Males have a higher mean IgE level than females ($P < .001$). IgE levels are higher among nonwhite patients than white patients ($P < .001$). Current smokers have higher IgE levels than past smokers or never smokers ($P < .001$). Among children, patients with severe asthma have a higher mean IgE level (280.2 IU/mL) than patients with moderate (145.8 IU/mL) or mild (137.8 IU/mL) asthma ($P < .001$). Among adults, patients with childhood-onset asthma have higher IgE levels (124.3 IU/mL [n = 1,348]) than patients with adult-onset asthma (65.7 IU/mL [n = 1,956]) ($P < .001$).

Conclusion: In patients with severe or difficult-to-treat asthma from the TENOR study, higher total IgE levels were observed in males, children, smokers, nonwhite racial/ethnic groups, and adults with childhood-onset disease. In addition, IgE levels are associated with asthma severity among younger patients.

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INTRODUCTION

Asthma is a multifactorial and complex chronic disease characterized by variable airflow obstruction and airway hyperresponsiveness.[1] Patients with asthma tend to have an increase in airway reactivity to a variety of stimuli, such as allergens, irritants, exercise, cold air, and viruses. Most patients with asthma have an allergic component to their disease.[2] Furthermore, atopy or allergy is considered the most important risk factor for developing asthma.[1,3]

IgE plays a key role in mediating the allergic response in asthma.[4] Epidemiologic studies have consistently shown that patients with asthma have elevated levels of IgE compared with nonasthmatic populations.[5–11] A number of factors have been shown to correlate with serum levels of IgE in both healthy individuals and patients with asthma.[12] Serum IgE levels are age related, with peak levels occurring during childhood, usually between the ages of 8 and 12 years, and typically decreasing thereafter.[8,9,11,13–18] In adults, serum IgE levels are higher in men than in women,[7,13–15,19,20] although differences by sex are not as well established in younger populations.[21] In addition, serum IgE levels may vary by race/ethnicity,[9,11,16,17] smoking history,[7,19,22,23] and asthma severity.[24–27]

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) is a large (>4,500) cohort of patients with severe and/or difficult-to-treat asthma. The primary objective of TENOR is to collect prospective data to better understand the natural history of asthma in the understudied severe asthma population. The objectives of this report are to describe the distribution of IgE levels in the entire TENOR cohort, in key demographic and clinical subgroups, and to examine the relationship of IgE to physician-evaluated asthma severity. The methods and baseline population characteristics of TENOR have been described elsewhere.[28]

METHODS

Design

TENOR is a prospective, observational, 3-year study of patients in the United States with severe or difficult-to-treat asthma. No experimental intervention is involved; participants continue to receive medications and treatments for their asthma as indicated by their asthma specialist. TENOR's design and protocol were approved by a central institutional review board and, when necessary, by the institutional review board at each site.

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Participants

TENOR participants are 6 years or older and considered by physician evaluation to have severe or difficult-to-treat asthma. Patients with mild or moderate disease were eligible for enrollment if their physician considered their asthma difficult to treat and they met the inclusion and exclusion criteria.[28] Patients had to be receiving care from their physician or health care practitioner for at least 1 year and had to be able to read and understand English. In addition, they must have had evidence of either frequent use of the health care system or high medication use or both. Patients were excluded if they were heavy smokers (>30 pack-years) or if they had a diagnosis of cystic fibrosis. All participants supplied written informed consent.

Demographic and Clinical Assessments

All data in this analysis were collected at the baseline study visit. TENOR physicians evaluated each participant's asthma severity and subjectively categorized patients as having mild, moderate, or severe disease. In addition, physicians reported whether their patient's asthma is considered difficult to treat based on specified parameters (ie, complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy). Demographic and clinical data collected by study coordinator interview and evaluation included age, sex, race, education level, and age of disease onset.

Measurement of IgE Levels

Total serum IgE levels were measured at baseline by each study site using any commercially available assay. All IgE assay tests used in TENOR have received 510 (k) Food and Drug Administration approval and are considered substantially equivalent in terms of both accuracy and precision. In addition, all total IgE assays are calibrated to the World Health Organization's Second International Reference Preparation for Human Serum IgE.

Statistical Analyses

The large sample size of TENOR permits relevant analyses, including key subgroups (eg, age, sex, race). Descriptive statistics were produced for demographic and baseline characteristics and were summarized by age group (children [aged 6–12 years], adolescents [aged 13–17 years], and adults [aged ≥18 years]). Adults were categorized by education level (low [high school diploma or less] or higher [more than a high school diploma]) and age at asthma onset (childhood onset [<18 years] and adult onset [≥18 years]).

The distribution of baseline IgE is positively skewed. Therefore, the geometric mean, rather than the arithmetic mean, was used to approximate the normal distribution for statistical inference and modeling. Comparison of IgE levels were performed by sex, age, race, smoking history, education level (for adults), adult vs childhood asthma onset (for adults), and physician-diagnosed asthma severity. Depending on the characteristic, either the F test or *t* test was used to compare IgE levels. No adjustments were made for multiple comparisons. All analyses were performed using SAS statistical software, version 8.02, for Windows (SAS Institute Inc, Cary, NC).

RESULTS

From January 2, 2001, to October 10, 2001, 4,923 patients were screened for inclusion in the study. Of these, 4,756 patients were enrolled and completed a baseline study visit (Table 1). Baseline characteristics of the TENOR study cohort are discussed in detail elsewhere.[28] In brief, 73.4% of the cohort is adult, 10.4% adolescent, and 16.2% pediatric. Most adult patients are female, whereas most adolescent and pediatric patients are male. In the overall cohort, 75.1% of subjects are white, 15.0% black, 6.4% Hispanic, and 1.5% Asian/Pacific Islander. Most adult patients enrolled in TENOR never smoked (73.1%), whereas 23.6% are past smokers and 3.4% are current smokers.

The baseline geometric mean IgE of the population (N = 4,512) is 106.6 IU/mL (95% confidence interval, 101.5–112.0 IU/mL). For both sexes, children and adolescents have higher mean IgE levels than adults (182.5, 223.8, and 85.2 IU/mL, respectively; $P < .001$). The distribution of IgE levels across 5-year age groups showed that younger patients have higher IgE levels than older patients for both sexes. Male patients have higher mean IgE levels than female patients across all of the 5-year age groups ($P < .001$) (Fig 1).

Overall, IgE levels are higher among nonwhite racial groups than whites: 90.2 IU/mL for whites (n = 3384), 187.8 IU/mL for blacks (n = 681), 143.9 IU/mL for Hispanics (n = 290), and 233.7 IU/mL for Asian/Pacific Islanders (n = 66) ($P < .001$) (Fig 2). Overall, no differences occurred in IgE levels between adults with low education and those with higher education (87.1 IU/mL [n = 967] and 84.6 IU/mL [n = 2,339], respectively). Results show higher IgE levels in nonwhites and lower levels in whites regardless of education level (nonwhites: 126.1 IU/mL [n = 290] for low and 133.5 IU/mL [n = 381] for higher education, $P = .65$; whites: 74.3 IU/mL [n = 677] for low and 77.5 IU/mL [n = 1958] for higher education, $P = .57$).

When evaluated by smoking history and sex in adult patients, IgE levels are higher among current smokers (161.3 IU/mL [n = 138]) than past smokers (83.4 IU/mL [n = 1066]) or never smokers (82.7 IU/mL [n = 2105]), although the number of current smokers was limited ($P < .001$) (Fig 3). This increase in IgE among smokers was observed in both sexes and in white and nonwhite patients.

When stratified by asthma severity as evaluated by the physician, the overall IgE geometric mean values were lower in patients with mild asthma (99.9 IU/mL [n = 138]) than in patients with moderate asthma (102.1 IU/mL [n = 192]) or severe asthma (112.0 IU/mL [n = 2171]). In children, IgE levels increase with increasing asthma severity. Pediatric patients with severe disease have higher mean IgE levels (280.2 IU/mL [n = 253]) than those with moderate disease (145.8 IU/mL [n = 435]) or mild disease (137.8 IU/mL [n = 38]) ($P < .001$). A similar trend is seen in adolescent patients

Table 1. Baseline Demographics of the TENOR Cohort

Demographic	Overall	Adults (≥18 y)	Adolescents (13–17 y)	Children (6–12 y)
Patients, No. (%)	4756 (100)	3489 (73.4)	497 (10.4)	770 (16.2)
Age, mean ± SD, y	38.9 ± 20.92	48.9 ± 14.85	14.5 ± 1.34	9.5 ± 1.88
IgE, geometric mean (95% CI), IU/mL	106.6 (101.5–112.0)	85.2 (80.5–90.1)	223.8 (196.4–255.1)*	182.5 (160.4–207.6)*
Sex, No. (%)				
Female	2,945 (62.2)	2,475 (71.2)	213 (42.9)	257 (33.5)
Male	1,792 (37.8)	999 (28.8)	283 (57.1)	510 (66.5)
Race/ethnicity, No. (%)				
White	3,555 (75.1)	2,769 (79.8)	323 (65.3)	463 (60.4)
Black	712 (15.0)	404 (11.6)	115 (23.2)	193 (25.2)
Hispanic	303 (6.4)	197 (5.7)	36 (7.3)	70 (9.1)
Asian/Pacific Islander	72 (1.5)	57 (1.6)	7 (1.4)	8 (1.0)
Other	91 (1.9)	44 (1.2)	14 (2.8)	33 (4.3)
Education level, No. (%)				
High school diploma or less	1,005 (29)	1,005 (29)	NA	NA
More than a high school diploma	2,461 (71)	2,461 (71)	NA	NA
Smoking history, No. (%)				
Never	3,454 (73.1)	2,207 (63.7)	483 (97.8)	764 (99.6)
Past	1,113 (23.6)	1,110 (32.0)	3 (0.6)	0 (0.0)
Current	159 (3.4)	148 (4.3)	8 (1.6)	3 (0.4)
Physician assessment of severity, No. (%)				
Mild	149 (3.2)	91 (2.6)	19 (3.8)	39 (5.1)
Moderate	2,285 (48.4)	1,595 (46.1)	237 (47.9)	453 (59.1)
Severe	2,285 (48.4)	1,771 (51.2)	239 (48.3)	275 (35.9)

Abbreviations: CI, confidence interval; NA, not applicable; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.
* $P < .001$ vs adults.

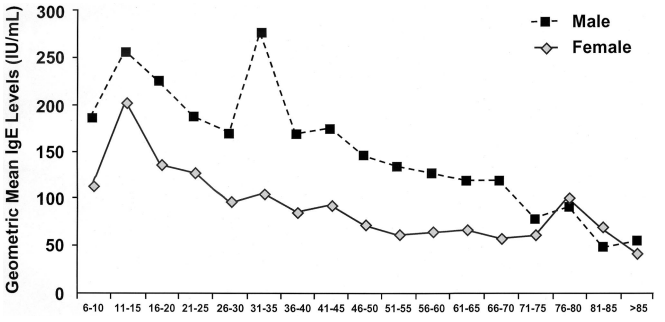

Figure 1. Distribution of IgE across 5-year age groups in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort by sex. $P < .001$ for children and adolescents vs adults. $P < .05$ for males vs females across all of the 5-year age groups.

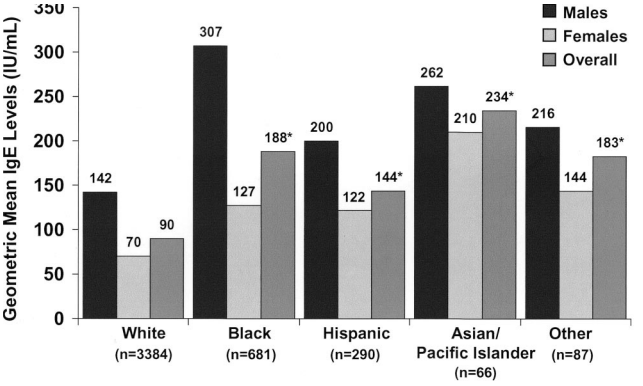

Figure 2. Geometric mean IgE levels by race and sex. Asterisk indicates $P < .001$ for all nonwhite racial/ethnic groups vs whites.

but did not reach statistical significance. Mean IgE levels in adults are not significantly different across the categories of disease severity (Fig 4).

We observed higher IgE levels in adult patients with childhood-onset asthma (124.3 IU/mL [n = 1,348]) compared with adult-onset asthma (65.7 IU/mL [n = 1,956]) ($P < .001$) (Table 2). In addition, a nonsignificant trend was apparent for increased disease severity in patients with childhood-onset asthma but not in those with adult-onset asthma.

DISCUSSION

TENOR is the largest observational study conducted of patients with severe or difficult-to-treat asthma with measured IgE levels. Although TENOR is not a population-based study, the cohort represents children, adolescents, and adults of diverse racial and ethnic backgrounds from widely distributed areas across the United States. With more than 4,500 participants with a measured IgE level at baseline, TENOR provides the largest database available to examine the relation-

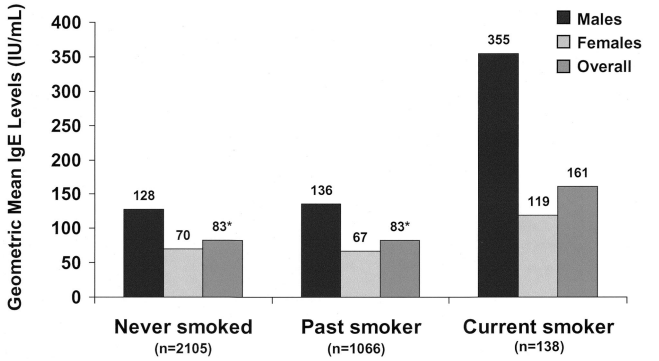

Figure 3. Geometric mean IgE levels by smoking history and sex in adult subjects. Asterisk indicates $P < .001$ for current smokers vs past or never smokers.

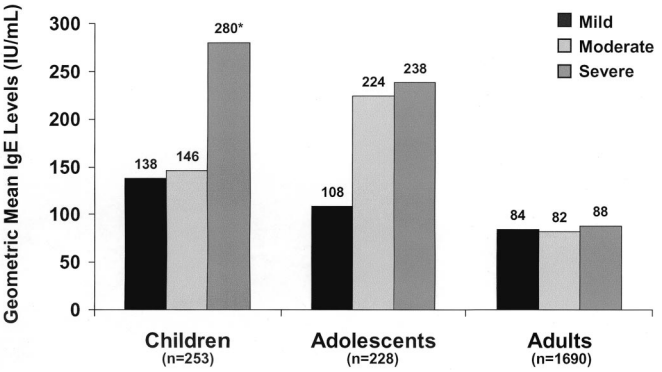

Figure 4. Geometric mean IgE levels by physician-evaluated asthma severity. Asterisk indicates $P < .001$ vs children with mild or moderate disease.

ships between demographic and clinical characteristics and IgE in patients with severe or difficult-to-treat asthma.

Consistent with the body of evidence from smaller studies, IgE levels in the TENOR population are elevated compared with other measured, normal, nonasthmatic populations.[5–9] The estimated mean total IgE level of the US general population (adults and children) is approximately 30 IU/mL.[9,13] In TENOR, the estimated mean IgE level of the overall population is 106.6 IU/mL. Because the TENOR cohort includes children, adolescents, and adults with severe or difficult-to-treat asthma, it is difficult to place these results in the context of other populations of asthmatic patients and atopic or allergic patients. In a small sample of asthmatic patients (n = 237) from a general population study, Burrows and colleagues[8] reported mean IgE levels of 224 IU/mL in patients aged 6 to 34 years, 117 IU/mL in those 35 to 54 years old, and 56 IU/mL in those 55 years or older. In a larger Tucson epidemiology study,[13] which consisted of a large community sample (n = >3,500) of patients 6 years and older, the mean IgE levels for male and female patients with a positive skin test result were 107.7 and 60.8 IU/mL, respectively. For both sexes in TENOR, children and adolescents have higher mean IgE levels than adults. Across all age groups, male patients in TENOR had higher mean IgE levels than female patients. This is consistent with other reports in the literature.[7,13–15,19,20]

In addition to sex, serum IgE level varies by ethnicity.[9,11,16,17] Grundbacher and Massie[11] reported higher levels of IgE in both nonallergic and asthmatic black individuals compared with nonallergic and asthmatic white individuals. Overall, IgE levels in TENOR were higher in nonwhite racial groups than in whites. The highest levels are found in blacks and Asian/Pacific Islanders. Although the subgroup composed of Asian/Pacific Islanders is small, these data are consistent with other reports that evaluated IgE levels in this racial/ethnic group.[29,30] Serum IgE levels in Hispanic patients are also higher than in whites.

No significant difference existed in IgE level in the overall TENOR cohort based on level of education. Education is a useful, if somewhat indirect, indicator of socioeconomic status. Furthermore, there is no difference in IgE levels within white and nonwhite subgroups when broken down by education level. It may be that the association between IgE and race/ethnicity observed in TENOR is due to unique asthma or allergy genes in different racial/ethnic groups[31–33] rather than differences in socioeconomic status, as has been hypothesized by some investigators, or to related factors, such as increased allergen exposures in inner-city environments.

Several studies in nonasthmatic populations or mixed populations of asthmatic and nonasthmatic patients have demonstrated that smokers have higher IgE levels than nonsmokers.[7,19,22,23,34] In one study of the risk factors for chronic airflow limitation and bronchial hyperresponsiveness, serum IgE levels were significantly higher in heavy smokers but not different among nonsmokers, ex-smokers, and current smokers.[35] Others report that serum IgE levels among smokers were not correlated with the amount smoked or the number of pack-years.[34] Higher IgE levels in smokers in TENOR are consistent with data in the literature that show increased IgE levels in smokers and those exposed to second-hand smoke[7,36–39] and is also consistent with data that show that exposure to environmental pollutants that include compounds present in cigarette smoke stimulates IgE production.[40–42]

When IgE levels of TENOR participants were examined in relationship to smoking status, it was found that IgE levels are higher in current smokers than past smokers or those who have never smoked. This relationship was consistent across subgroups of race and sex. The strong relationship seen in the large TENOR cohort may be a consequence of these patients all having asthma. There is a low likelihood that patients in TENOR had chronic obstructive pulmonary disease, a condition frequently misdiagnosed as asthma, because heavy smokers (>30 pack-years) were excluded from the study.

Although some studies have reported an association between IgE and asthma severity,[24–27] others have not.[43] A longitudinal study in Melbourne, Australia, of asthmatic children studied at 7, 10, and 14 years of age reported mean serum IgE level by grade of disease severity.[24] Results showed higher IgE levels in patients with more severe and

Table 2. Relationship Among Age at Onset of Asthma, Physician-Rated Disease Severity, and Mean Geometric IgE in Adult Patients in TENOR

	No. of patients	IgE, geometric mean (95% CI), IU/mL	*P* value
Onset of asthma			<.001
Childhood	1,348	124.3 (113.8–135.7)	
Adult	1,956	65.7 (61.2–70.5)	
Asthma severity			
Childhood onset			.17 for trend
Mild	36	99.0 (69.3–141.4)	
Moderate	610	118.6 (104.5–134.5)	
Severe	698	131.2 (115.6,149.0)	
Adult onset			.90 for trend
Mild	45	74.2 (49.0–112.3)	
Moderate	917	64.5 (58.2–71.6)	
Severe	988	66.3 (60.0–73.3)	

Abbreviations: CI, confidence interval; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.

persistent asthma compared with those with mild, episodic asthma.

Overall, TENOR's pediatric patients with severe asthma have higher IgE levels compared with children with moderate or mild asthma. This finding may be attributable to the fact that TENOR, compared with many other studies, has a sufficiently large sample size of pediatric patients with severe asthma. Although the severity of the TENOR population may have made it possible to detect the relationship between asthma and severity in the younger populations, more detailed investigation of the relationship between severity and asthma in TENOR is limited by the comparatively few patients with mild asthma in the study.

The TENOR study examines the relationship between total IgE level and severe or difficult-to-treat asthma but does not provide data on specific IgE levels. In addition, IgE levels were measured once at baseline, and any conclusions extrapolated from these data assume that the total IgE level remains stable over time in this cohort. Approximately 3% of patients in TENOR reported vocal cord dysfunction (VCD) as a comorbidity. Mean IgE levels in patients with VCD in TENOR are lower than in patients without this comorbidity but higher than in nonallergic controls.[9,13] We cannot exclude the possibility that some patients in TENOR have unidentified VCD that has been misdiagnosed as asthma. Patients with VCD without asthma typically have low IgE levels.[44] Although the inclusion of a small subset of patients with unidentified VCD could dilute the association between asthma and IgE in TENOR, this appears unlikely given the large size of the cohort.

The association of total IgE level with asthma severity may reflect a role for specific IgE-mediated allergic reactions in contributing to severity. It is also plausible that total IgE concentrations may reflect the T_H2 milieu characteristic of asthmatic inflammation, with high concentrations of interleukin 4 (IL-4) and IL-13,[45] cytokines that mediate the immunoglobulin isotype switch to IgE. In the presence of IL-4 and IL-13, any humoral immune response that is occurring is likely to be associated with generation of IgE to the antigen. In this scenario, a high total IgE concentration may correlate with the severity of the T_H2 cytokine milieu and the degree of inflammation.[45]

TENOR data show higher IgE levels in adult patients with childhood-onset asthma than in those with adult-onset asthma, suggesting that patients with childhood-onset asthma may have more highly "allergic" or T_H2-driven disease. These findings from TENOR, in addition to recent data from Miranda and colleagues[46] showing immunologic and pathologic differences between early- and late-onset subgroups, highlight the concept that adult-onset asthma may represent a distinct mechanism of action and the importance of examining age of asthma onset in populations with severe asthma.

In conclusion, the TENOR study provides the unique opportunity to examine the natural history of asthma in the understudied severe asthma population. Higher IgE levels were observed in this population of asthmatic patients compared with nonasthmatic or nonallergic populations. We observed higher IgE levels among male patients, children, smokers, nonwhite racial/ethnic groups, and adults with childhood-onset asthma. In addition, IgE levels are associated with asthma severity among younger patients. Additional planned TENOR analyses will examine the relationship between IgE levels and allergic status, lung function, and IgE levels in patients with allergic comorbidities.

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