

Total IgE in urban Black South African teenagers: The influence of atopy and helminth infection

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Total IgE levels are usually elevated in allergic diseases, being highest in atopic eczema, followed by atopic asthma and allergic rhinitis. Genetic factors are believed to play a role in total IgE levels, with higher levels seen in Black African subjects. Total IgE is also raised in parasite infection. Thus, the higher total IgE levels in Black Africans could be because of environmental rather than genetic factors. Few studies have investigated the usefulness of total IgE levels in the evaluation of atopy in Black Africans. The objective of this study was to determine the total IgE levels in unselected urban Black African high school children and to correlate this with atopy and ascaris sensitization. Atopic status was assessed by means of specific allergen sensitization (skin prick tests to eight inhalant and four food allergens), self-reported asthma and bronchial hyper-responsiveness measured by methacholine challenge. Ascaris sensitization was assessed by means of ascaris IgE measured by CAP-RAST. Total IgE levels were markedly skewed toward the left and were not distributed in a Gaussian or a log-normal distribution. Skin prick tests were positive for aeroallergens in 32.3% of subjects. Thirty four percent had elevated ascaris IgE. Total IgE was higher in atopic vs. non-atopic subjects and correlated with the number of positive skin prick tests, self-reported asthma and bronchial hyper-responsiveness. Subjects without allergy (or) atopy had a median total IgE of 80–90 kU/I. In addition total IgE correlated with ascaris IgE. Subjects with no ascaris sensitization had median total IgE of 77.1 kU/l. Subjects with neither atopy/asthma nor ascaris sensitisation had a median total IgE of 69.9 kU/I, similar to the levels seen in people of other genetic origins. This study suggests that helminthic infection rather than genetic differences, may be the major determining factor of IgE levels in certain populations.

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IgE was first characterized and purified by Ishizaka and Ishizaka (1) in the 1960s. IgE levels are usually elevated in allergic diseases, being highest in atopic eczema, followed by atopic asthma and allergic rhinitis. Genetic factors are believed to play a role in total IgE levels, with higher levels seen in Black African subjects (Table 1). In Black African subjects, there is little or no difference in total IgE levels between asthmatics and controls (2–4). Early research in South Africa (5) found that IgE is much higher in

Black African and mixed race subjects compared with Caucasians, but the difference in total IgE levels between atopic and non-atopic subjects was significant only in Caucasian subjects. A subsequent study (6) on cord blood IgE in Black African, Caucasian and mixed race subjects showed elevated cord blood IgE concentrations in Black Africans independently of an atopic family history or maternal ascariasis (measured with ascaris IgE). This has perpetuated the notion that Black African subjects have

Table 1. IgE levels in populations with different genetic origin and area of residence

Genetic group	Area	Total IgE (kU/l)
Caucasian (28)	Sweden	24*
Caucasian (29)	USA	67†
Caucasian (30)	USA	41*
Filipino(30)	USA	113*
African American (31)	USA	70*
Black African(2)	Rural Tanzania	3174*
Black African(4)	Urban Ethiopia	1347‡
Black African(3)	Rural Gambia	962*
Black African(3)	Urban Gambia	368*
Black African(7)	Rural 'Rhodesia'	1613†
Black African(7)	Urban 'Rhodesia'	350†
Black African(5)	South Africa	739‡
Mixed race(5)	South Africa	201‡
Caucasian(5)	South Africa	42‡

*Geometric mean of log-transformed data.

†Mean of non-transformed data.

‡Median.

a genetic propensity to raised IgE levels. Currently local laboratories use total IgE ranges that are ethnically based and the usefulness of total IgE levels in the assessment of atopy has been questioned in Black Africans. Early studies also documented urban–rural differences in total IgE levels among Black African subjects elsewhere in Africa (3, 7). Total IgE is also raised in parasite infection, and early studies of Black African subjects may have had higher rates of helminthic infestation. Thus, the higher total IgE levels in Black Africans could be due to environmental rather than genetic factors. This casts doubt on the validity of separate ethnically based reference ranges. A recent study (8) confirmed that in the United Kingdom, children of Afro-Caribbean, White and Bangladeshi origin had similar IgE levels, but noted that in all groups, levels were higher than those previously published. The applicability of these data to the South African context is limited because of different genetic origins and different environmental factors.

Aim

The objective of this study was to determine the total IgE levels in unselected urban Black African high school children and to correlate this with atopy and sensitization to ascaris. Atopic status was assessed by means of specific allergen sensitization (skin prick tests), self-reported asthma and bronchial hyper-responsiveness measured by methacholine challenge. Ascaris sensitization was assessed by means of ascaris IgE measured by CAP-RAST (Phadia, Uppsala, Sweden). Total IgE levels were subanalyzed according to atopic status and ascaris sensitization to establish

ranges of total IgE in atopic subjects, ascaris sensitized subjects, and non-atopic, non-ascaris sensitized subjects.

Methods

Two hundred and twenty Urban Xhosa children (mean age 17 yr) attending a high school in Mowbray, Cape Town were studied. Total IgE levels, ascaris specific IgE (Phadia, Uppsala, Sweden) and skin test reactivity to housedust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass mix, Bermuda grass, mould mix, cat, dog, German cockroach, egg white, milk, peanut and potato (ALK[®]-ABELLO, Madrid, Spain) were determined. Skin prick tests were deemed positive if wheal size was 3 mm or more greater than the negative control. Questionnaires – were administered in the preferred language (English or Xhosa). Bronchial hyper-responsiveness was assessed by a novel method based on the Yan protocol (9) using hand-blown DeVilbiss no 45 glass nebulisers. Saline diluent was administered and then methacholine in doubling dosages from 0.0015 mg to 0.5 mg which attained a cumulative dose of 1.1675 mg. Bronchial hyper-responsiveness (BHR) was defined as a fall in FEV1 of greater or equal to 20% at any dose below the maximal dose administered.

Results

Total IgE levels were markedly skewed toward the left and were not distributed in a Gaussian or a log-normal distribution (Fig. 1). Mean total IgE was 307.7 kU/L. The median was 106 kU/l and the interquartile range 50.4–288 kU/l.

Skin prick tests were positive for aeroallergens (Table 2) in 71 (32.3%) subjects; 7.4% were

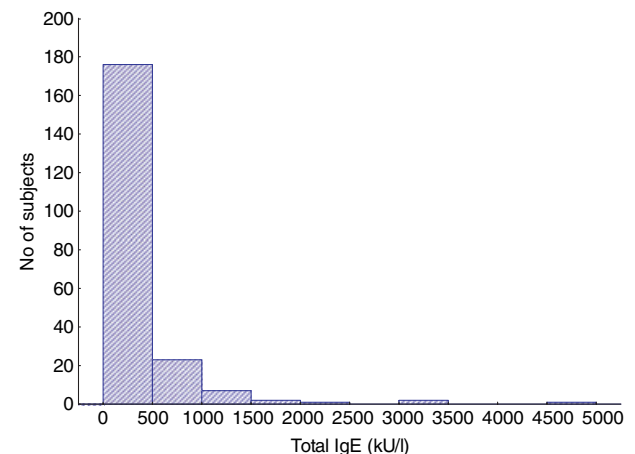


Fig. 1. Distribution of total IgE levels.

Table 2. Positive skin prick tests to aeroallergens

Allergen	N	Percent of total subjects
<i>Der p</i>	54	24.5
<i>Der f</i>	51	23.2
<i>Bla g</i>	38	17.3
Grass mix	12	5.5
Bermuda grass	10	4.5
Dog dander	6	2.7
Cat	5	2.3
Mould mix	2	0.9

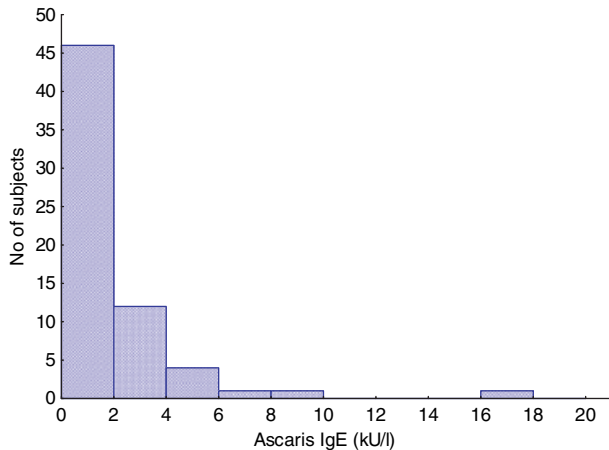


Fig. 2. Distribution of ascaris IgE.

monosensitive and 25.9% had two or more positive skin prick tests; 137 (66.7%) had negative skin prick tests. The most common sensitivities were to *Dermatophagoides pteronyssinus* (24.5%), *Dermatophagoides farinae* (23.2%), and German cockroach (17.3%). Skin prick tests were positive for food allergens in 12 (5.4%) subjects, most commonly to egg white ($n = 7$; 3.2%). Seventy-five subjects (34.1%) had elevated (>0.35 kU/l) ascaris IgE; in 58 (28%) the levels were class 1 (0.35–3.5 kU/l) and class 2 (3.5–17.5 kU/l) in only 7 (3%). Ascaris specific IgE was markedly skewed toward the left (Fig. 2) and was not distributed in a Gaussian nor a log-normal distribution. In those with detectable levels of ascaris specific IgE, the median value was only 0.9 kU/l (interquartile range 0.5–2.3 kU/l) and the highest level was 17.5 kU/l. Ascaris IgE was negative (<0.35 kU/l) in 145 (69%) subjects. Twenty subjects (8.9%) reported symptoms of asthma. Thirty two (15.5%) demonstrated bronchial hyper-responsiveness.

Correlations

Total IgE was higher in atopic vs. non-atopic subjects and correlated with the number of

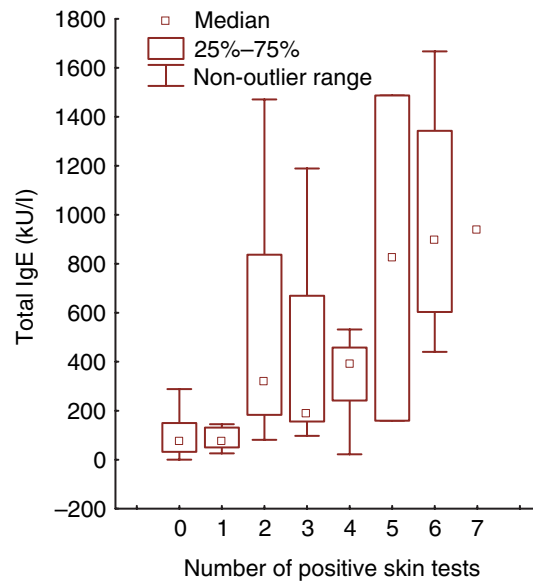


Fig. 3. Total IgE vs. positive skin prick tests.

positive skin prick tests (Fig. 3: Kruskal–Wallis ANOVA < 0.0001). Total IgE was raised significantly in subjects with two or more positive skin prick tests (median 388 kU/l, interquartile range 163–890 kU/l), but there was no significant difference in total IgE between subjects with negative tests or one positive skin prick test (median 76.7 kU/l, interquartile range 36.2–145 kU/l).

Median total IgE was higher in subjects with positive skin prick tests to *Der p* (306 vs. 78.8 kU/l; $p < 0.0001$), *Der f* (406 vs. 79.4 kU/l; $p = 0.01$), cockroach (316 vs. 85.2 kU/l; $p < 0.0001$), grass mix (71 vs. 94.7 kU/l; $p = 0.0001$), Bermuda grass (774 vs. 95.1 kU/l; $p = 0.0001$) and cat (388 vs. 97.9 kU/l; $p = 0.02$). Of note, total IgE was lower (701 vs. 107 kU/l; not statistically significant) in subjects with a positive ($n = 6$) compared with a negative skin test to dog. Total IgE was also higher in subjects with a positive skin prick test to cow's milk ($n = 4$, $p = 0.02$), but not in those with positive skin tests to egg white ($n = 7$) or peanuts ($n = 4$).

Total IgE correlated with ascaris IgE (Fig. 4). Total IgE was higher in those with raised ascaris IgE (Kruskal–Wallis $p < 0.0001$); median 397.5 kU/l (interquartile range 142–782 kU/l) for class 1 and 1019 kU/l (interquartile range 417 kU/l to 3330 kU/l) for class 2. In those with undetectable ascaris specific IgE, the median total IgE was 77.1 (interquartile range 32.1–139), within the normal range for age currently given for Caucasian subjects.

Subjects with self-reported asthma had a median total IgE of 324.5 kU/l (interquartile

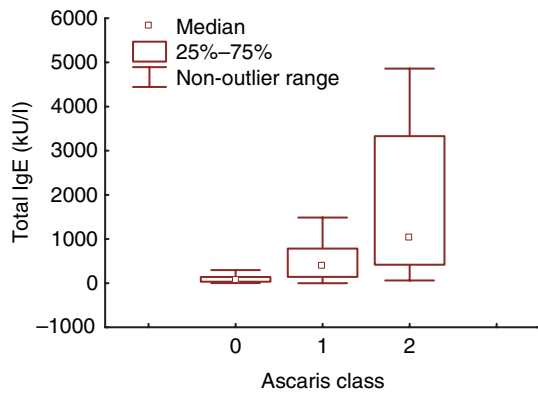


Fig. 4. Total IgE vs. ascaris IgE.

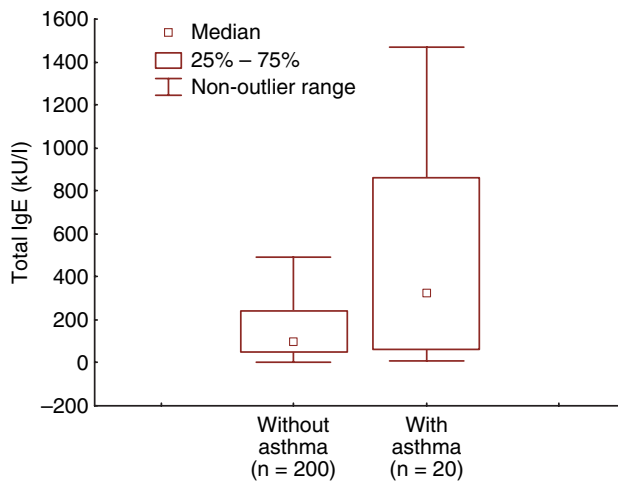


Fig. 5. Total IgE vs. self-reported asthma.

range 61.25–863.5 kU/l) compared with 95.4 kU/l (interquartile range 49.9–242 kU/l) in those without asthma symptoms (Fig. 5: Kruskal–Wallis $p = 0.025$). Subjects with bronchial hyper-responsiveness (BHR) to methacholine challenge had a median total IgE of 214 kU/l (interquartile range 118–826 kU/l) compared with 91.5 kU/l (interquartile range 44.6–236 kU/l) in those without BHR (Fig. 6: Kruskal–Wallis $p = 0.0002$) (Fig. 7).

Subjects with neither atopy/asthma (2 or more positive skin tests, bronchial hyper-responsiveness or asthma history) nor ascaris sensitisation had a median total IgE of 69.9 kU/l (interquartile range 28.2–109) (Figure 7).

Discussion

This study suggests that environment is the major factor determining a population's specific IgE range. The median total IgE was 106 kU/l (interquartile range 50.4–288 kU/l).

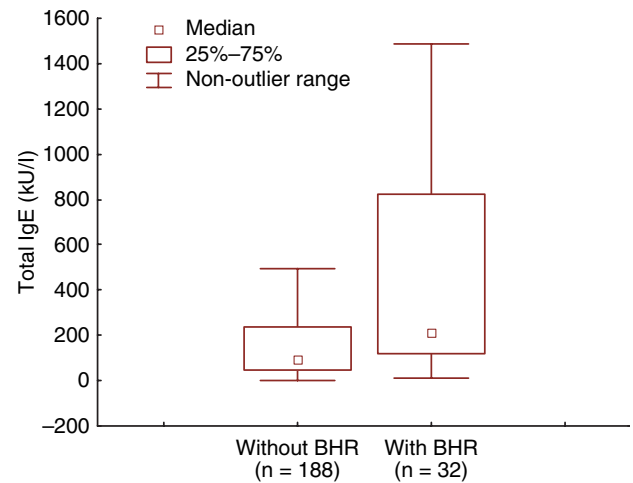


Fig. 6. Total IgE vs. bronchial hyper-responsiveness (BHR).

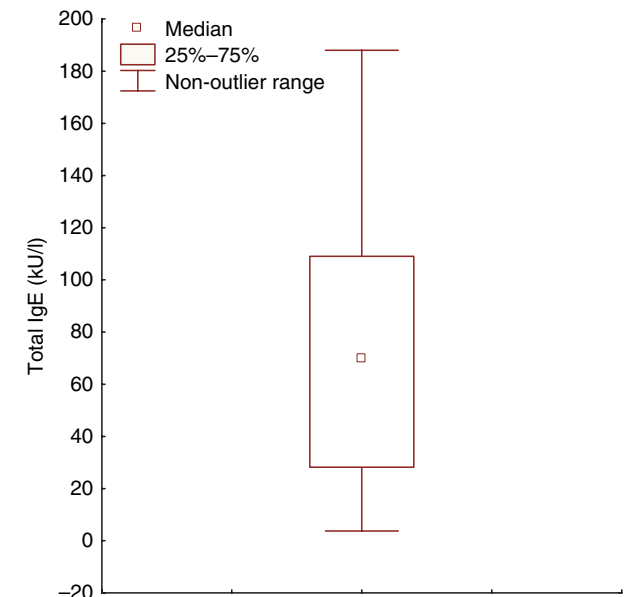


Fig. 7. Total IgE in subjects with neither atopy/asthma nor ascaris sensitisation.

Total IgE correlated well with atopy demonstrated by positive skin prick tests to aeroallergens. In addition total IgE correlated well with a prior history of asthma as well as bronchial hyper-responsiveness measured by methacholine challenge. Subjects with one or no skin prick test positive had a median of 76.7 kU/l, subjects with no history of asthma levels of 95.4 kU/l and subjects with negative methacholine challenge levels of 91.5 kU/l. There was a low incidence of subjects with raised ascaris IgE, but in these subjects total IgE was raised well out of the 'normal' range. Raised IgE levels were most marked (median 1019 kU/l) with class 2 ascaris

sensitization, followed by class 1 ascaris sensitization and skin prick test reactivity (about 400 kU/l), followed by a history of asthma (324.5 kU/l) and finally by bronchial hyper-responsiveness (214 kU/l). Subjects with no ascaris sensitisation had a median total IgE of 77.1 kU/l. Subjects without atopy/asthma had median total IgE of approximately 80–90 kU/l. Subjects with neither atopy/asthma nor ascaris sensitisation had a median total IgE of 69.9 kU/l (interquartile range 28.2–109), similar to the levels seen in people of other genetic origins.

The interactions between parasites and allergy can be postulated to occur at various levels. At the genetic level, evidence supports the hypothesis that relatively hostile ancestry conditions seen in tropical climates have caused genetic selection for strong pro-inflammatory Th2 immune responses that provide resistance to infectious diseases such as helminthic infections (10, 11). On migrating to temperate regions, pronounced pro-inflammatory responses would have been less important and selected against because of increased mortality from overly vigorous responses to harmless environmental agents (11). This hypothesis is supported by the observation that pro-inflammatory alleles in several genes involved in inflammation are more prevalent in populations with long-term tropical ancestry than those with long-term residence in temperate regions including variants associated with raised serum IgE levels (12–14). Of these polymorphisms, the FcεR1-β polymorphism, which is the β chain of the high affinity IgE receptor has been shown to be more frequent in black South African asthmatics than white South African asthmatics (15). In addition, when populations of tropical genetic origin relocate to a temperate region, they have a higher incidence of allergic inflammatory diseases than the local populations (16–18). Thus, these ethnic group-based differences in allele frequencies could be expected to lead to raised IgE levels in some genetic groups over others.

In addition to these effects, exposure to parasites at certain critical stages of immune maturation may be postulated to alter the Th1/Th2 balance or induce regulatory T-cells. Finally parasitic infestation itself causes marked immune responses such as eosinophilia, increases in specific IgE (19), raised total IgE and raised parasite specific immunoglobulin G4. The first two clearly favor the host but some immune responses may favor the parasite. Parasites are thought to have evolved the ability to generate polyclonal non-specific IgE to evade host immunity by saturating IgE receptors (20). This blocks

the cross-linking of parasite specific IgE on mast cells and therefore prevents their degranulation. Hagel et al.(19) found that in an area of high ascaris prevalence, very high total IgE was associated with an increased risk of reinfection after successful treatment. In another study (21), her group found a negative correlation between total IgE and antigen specific IgE (including ascaris IgE) as well as skin test reactivity. In general, anti-parasite IgE antibodies are low in children who are continually reinfected and high in adults who remain uninfected (22).

Parasitized subjects may be protected from atopy by blocking cross linking of allergen specific IgE (23) by parasite induced raised total IgE. Hence, in the presence of parasite infection, the accuracy of assessing atopy is impaired. This situation is further complicated by anti-helminthic treatment in which a drop in total IgE is accompanying by increased skin prick reactivity to inhalant allergens (24, 25). A weakness of the current study was the reliance on ascaris specific IgE as a marker for helminthic sensitization, as financial constraints precluded the measurement of IgG4 and the performance of serological tests for other parasites. In addition, collection of stool samples for confirmation of infection was impractical in this setting.

Total serum IgE is generally of limited value as a diagnostic test for atopic disease (26), although it may be helpful in the assessment of wheeze in young children, as it helps to discriminate transient from persistent wheezers. Results of our study suggest that the usefulness of total IgE estimation in the assessment of an individual's atopic status depends more on the likelihood of helminthic infection, rather than on ethnic differences in IgE levels. In this urban black South African population, total IgE levels were similar to other populations, questioning the need for ethnic group specific reference values. Interpretation of IgE levels should take into account the local environment and risk of parasite infestation. Measurement of ascaris specific IgE in those with high total IgE levels, use of the phadiatop (27) as a screening test, or testing for specific IgE tests against individual allergens would be more useful for diagnosis of allergic disease.

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