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Serum total IgE levels in a representative sample of a Greek population

I. Correlation with age, sex, and skin reactivity to common aeroallergens

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The distribution of IgE in a large randomly stratified Greek population sample was determined in 1187 subjects (793 men and 394 women) aged between 20 and 60 years. Skin prick testing was performed and serum total IgE expressed in iu/ml was measured by Phadebas PRIST: the data are presented as the geometric mean. Subjects were classified as atopic (257 men, 118 women) and nonatopic (536 men, 276 women) according to the results of skin testing with various aeroallergens. At any age, atopic males (120.5 vs 38 iu/ml) and females (99.8 vs 29.3 iu/ml) had higher mean IgE levels, as compared to nonatopic subjects ($P < 0.0001$). In our adult nonatopic sample, IgE levels did not differ with age ($P > 0.05$). At any age, nonatopic males had higher (38 iu/ml) mean IgE levels than nonatopic females (29.3 iu/ml) ($P < 0.05$). The comparison of normal IgE values (nonatopic subjects) from this study with those reported by other investigators revealed that Greek adult males and females had higher IgE levels than populations from other nations. Our results represent the first report on reference values regarding serum total IgE in Greek adults.

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It was in 1967 that Ishizaka (15) in the United States and Johansson et al. (17) in Sweden almost simultaneously isolated and characterized serum immunoglobulin E (IgE).

Increased levels of total serum IgE have been reported primarily in atopic diseases, such as respiratory allergies (allergic rhinoconjuctivitis, bronchial asthma), allergic bronchopulmonary aspergillosis, and atopic dermatitis. IgE is also increased in diseases such as parasitic infections (mostly those caused by helminths), immunodeficiences (Wiskott-Aldrich syndrome, hyper-IgE syndrome), viral infections (respiratory syncytial virus, Epstein-Barr virus, etc.), and neoplasms (Hodgkin's disease, IgE-myeloma, lung cancer) (28).

Knowledge of IgE levels is clinically useful in the following instances (28): 1) identification of subjects with atopic disease in a population with symptoms similar to those observed in allergic patients, 2) prediction of the development of an allergic disease in infants, 3) follow-up and evaluation of IgE-immune response in atopic patients undergoing therapy and specific hyposensitization, 4) diagnosis and follow-up of patients with allergic bronchopulmonary aspergillosis, 5) evaluation of patients with immunodeficiences, and 6) diagnosis and follow-up of patients suffering from parasitic infections.

To evaluate the IgE levels, one must be familiar with the normal range of this immunoglobulin's levels. Establishment of the normal values of IgE is sometimes a complex process: factors such as the presence or absence of an allergic disease, and differences in age, sex, or race, as well as the laboratory assay employed, interfere with the evaluation of IgE (3, 4, 11, 27).

Up to now, there have been no scientific reports defining the normal IgE levels in the general Greek population. As a result, there are no reference values in Greek literature to compare with the scientific data existing for children (19, 20), adolescents (13), and adults (3, 4, 14, 24, 29) from other countries.

The purpose of our study was to establish the normal range of serum total IgE levels in a representative sample of Greek adults in relation to their atopic predisposition, as defined from skin testing with a battery of common aeroallergens, and their age and sex.

Material and methods

From November 1988 to March 1989, 1137 subjects, 793 men (M) and 394 women (W), aged from 20 to 60 years, were studied. The age distribution, in 5-year steps, of the subjects submitted to examination was the following: 20–24 years (M = 130, W = 96), 25–29 years (M = 138, W = 79), 30–34 years (M = 131, W = 80), 35–39 years (M = 116, W = 36), 40–44 years (M = 106, W = 40), 45–49 years (M = 97, W = 17), and over 50 years (M = 75, W = 46).

All subjects derived from ground personnel (officers, privates, and civilians) of the Greek Air Force. Their examination took place during their scheduled 2-year checkup in the Department of Periodic Medical Examinations held at the 251th Air Force General Hospital of Athens. Since the personnel examined originated in different geographical parts of Greece and lived under similar socioeconomic conditions, this sample can well be considered representative.

All subjects submitted to complete clinical, hematological, electrocardiological, and chest X-ray examination and appeared, in general, to be healthy. None of the men and women examined had been taking medication for a long period, while subjects with recent parasitic infection were excluded from the study.

Skin tests (ST) performed with a selected battery of 11 common aeroallergens (Allergopharma, Germany), consisting of grasses, weeds, *Parietaria*, olive, house dust, *Dermatophagoides pteronyssinus*, *D. farinae*, cat, dog, *Alternaria*, and *Aspergillus*. Positive (histamine – 1 g/l) and negative (normal saline) controls were also included in order to check the reactivity of the skin. Allergen selection was based on their frequency in the Greek environment (1, 8). Skin tests were performed by the same investigator, at the same time of the day (in the morning), on the flexor surface of the right forearm by the skin prick method described by Pepys (3). Skin test evaluation was made by calculating the mean diameter (d) in mm of the wheal developed after 20 min. When the negative control was accompanied by a positive wheal reaction, the mean diameter of this reaction was deducted from the mean diameter of the wheals of the remaining aeroallergens applied. Subjects with dermographism were excluded. A wheal with a mean diameter $\geq$ half the diameter of the histamine wheal formation was considered positive (23).

Depending on the results of skin tests, the personnel were divided into two groups:

1. The atopic (A) group, comprising those with one or more positive skin tests together with symptoms of respiratory allergy: those without allergic symptoms despite their positive reactions were also included in this group.
2. The nonatopic (NA) group, comprising those with negative skin tests and no evidence of allergic disorders.

To determine the serum total IgE levels, blood samples were centrifuged and the sera obtained were stored at −20°C. For evaluation of total IgE a direct radioimmunoassay in two rows (Phadebas® IgE PRIST, Pharmacia, Sweden) was employed and the mean value calculated. Data were expressed in international units per milliliter (iu/ml). In 53 patients with a wide deviation between the two counts, a new determination of the serum total IgE was made.

A computer was used for development and classification of the patients' data and statistical analysis of the results obtained. Since the frequency distribution of the IgE levels appeared to be strongly asymmetrical, a logarithmic transformation ($\log_{10}$) was applied; the results were expressed as antilogarithms or geometrical means (GM) with standard deviation (SD).

To distinguish the statistically significant and nonsignificant correlations between the parameters studied, both t-test and analysis of variance were applied.

Results

Of the 793 male subjects studied, 257 (32.4%) were atopic and 536 (67.6%) nonatopic. In the atopic group the highest incidence of atopy was observed in the 20–24-year group (38.5%), though a second peak was present in the 30–34-year group (35.1%). The lowest incidence was observed in the > 50-year group (25.3%).

Of the 394 women studied, 118 (29.9%) were classified as atopic and 276 (70.1%) as nonatopic. In the atopic group the highest incidence of atopy was observed in the 25–29-year group (36.7%), and the lowest in the > 50-year group (21.7%).

Table 1 shows the total IgE levels (mean value log ± SD and GM ± 1 SD + 2 SD) according to age groups in nonatopic men and women. The correlations were not statistically significant (analysis of variance: $P = 0.990$ and $P = 0.560$, respectively). It is obvious that in all age groups, nonatopic men experienced higher IgE geometric means, as compared to nonatopic women.

Table 2 presents the IgE levels (mean value log ± 1 SD + 2 SD) in various age groups in atopic male and female subjects. In all age groups except the 35–39-year, atopic men experienced higher IgE geometric means than atopic women.

As clearly shown in Table 3, the geometric mean of IgE in all nonatopic men was higher than the

Table 1. Serum total IgE levels (iu/ml) (mean value log±SD, GM±1 SA+SD) according to age groups (5-year steps) in nonatopic men (M) and women (W)

Age (yr)	n	Mean value log±SD	GM	GM−1 SD	GM+1 SD	GM+2 SD
20–24	(M=80)	1.559±0.460	36.2	12.6	104.5	301.3
	(W=66)	1.531±0.510	34.0	10.5	109.9	355.6
25–29	(M=98)	1.700±0.470	50.1	17.0	147.9	436.5
	(W=50)	1.505±0.510	32.0	9.9	103.5	334.9
30–34	(M=85)	1.588±0.440	38.7	14.0	106.7	293.7
	(W=55)	1.423±0.460	26.5	9.2	76.4	220.2
35–39	(M=76)	1.592±0.420	39.0	14.9	102.8	270.3
	(W=26)	1.475±0.460	29.9	10.4	86.0	248.3
40–44	(M=71)	1.576±0.480	37.7	12.5	113.8	343.5
	(W=30)	1.427±0.330	26.7	12.5	57.1	122.1
45–49	(M=70)	1.483±0.420	30.4	11.6	80.0	210.3
	(W=13)	1.399±0.550	25.0	7.0	88.9	274.7
>50	(M=56)	1.504±0.380	31.9	13.3	76.6	183.6
	(W=36)	1.420±0.480	26.3	8.7	79.4	239.8

Analysis of variance
Men: $P=0.990$ ($P>0.05$)
Women: $P=0.560$ ($P>0.05$)

Table 2. Serum total IgE levels (iu/ml) (mean value log±SD, GM±1 SA+SD) according to age groups (5-year steps) in atopic men (M) and women (W)

Age (yr)	n	Mean value log±SD	GM	GM−1 SD	GM+1 SD	GM+2 SD
20–24	(M=50)	2.150±0.460	141.3	49.0	407.4	1174.9
	(W=30)	2.010±0.330	102.3	47.9	218.8	467.7
25–29	(M=40)	2.031±0.470	107.4	36.4	317.0	935.4
	(W=29)	2.030±0.410	107.2	41.7	275.4	707.9
30–34	(M=46)	2.125±0.450	133.4	47.3	375.8	1059.3
	(W=25)	2.024±0.540	105.7	30.5	366.4	1270.6
35–39	(M=40)	2.111±0.430	129.1	48.0	347.5	935.4
	(W=10)	2.170±0.430	147.9	55.0	398.1	1071.5
40–44	(M=35)	2.093±0.490	123.9	40.0	382.8	1183.0
	(W=10)	1.963±0.570	91.8	24.7	341.2	1267.7
45–49	(M=27)	2.004±0.570	100.9	27.2	375.0	1393.2
	(W=4)	1.641±0.410	43.8	17.0	112.5	289.0
>50	(M=19)	1.933±0.600	85.7	21.5	341.2	1358.3
	(W=10)	1.822±0.590	66.4	17.0	258.2	1004.6

geometric mean of all nonatopic women (38 iu/ml vs 29.3 iu/ml). This correlation was considered statistically significant (t-test: $P=0.0013$). On the other hand, the IgE geometric mean in all atopic males was higher than that in all atopic women (120.5 iu/ml vs 99.8 iu/ml). Nevertheless, this correlation was considered statistically nonsignificant (t-test: $P=0.1169$). It is clear from Table 3 that the geometric mean of IgE in all atopic men was higher than that of all nonatopic men (120.5 IU/ml vs 38 IU/ml). The difference is statistically significant (t-test: $P<0.0001$). In all age groups, atopic women experienced much higher IgE geometric means than nonatopic women. Table 3 shows that the geometric mean levels of IgE in all atopic women were higher than those of nonatopic women (99.8 iu/ml vs 29.3 iu/ml). The difference observed was statistically significant (t-test: $P<0.0001$).

Table 3. Serum total IgE levels (iu/ml) (mean value log±SD, GM±1 SA+SD) in all atopic and nonatopic men and women studied

Subjects examined	Mean value log±SD	GM	GM−1 SD	GM+1 SD	GM+2 SD
Men nonatopic (n=536)	1.580±0.450	38.0	13.5	107.2	302.0
Women nonatopic (n=276)	1.467±0.479	29.3	9.7	88.3	266.0
Men atopic (n=257)	2.081±0.486	120.5	39.4	369.0	1129.8
Women atopic (n=118)	1.999±0.461	99.8	34.5	288.4	883.7

IgE (iu/ml) in nonatopic men and women: t-test, $P=0.013$ ($P<0.05$)*
IgE (iu/ml) in atopic men and women: t-test, $P=0.1169$ ($P>0.05$)
IgE (iu/ml) in atopic and nonatopic men: t-test, $P<0.0001$ ($P<0.05$)*
IgE (iu/ml) in atopic and nonatopic women: t-test, $P<0.0001$ ($P<0.05$)*

Discussion

Scientists from various countries have attempted to define the normal range of IgE levels in healthy individuals, but many of these studies are deficient, mainly for two reasons. First, the new, more sensitive methods of detection of very low IgE levels (11, 16) were not employed, and, second, the population samples studied were not representative (5, 9, 24, 26, 27). As a result, only a small number of studies from North America and European countries referring to children (19, 20), adolescents (13), and adults (3, 4, 14, 29) provide reliable information about the normal range of IgE.

Up to now no similar investigation has been made in Greece. The result has been that IgE levels in the Greek population have been evaluated in comparison with the normal variation of IgE in other countries. That IgE levels may differ from country to country (11, 21) urged us to determine for the first time the normal range of serum total IgE in a representative sample of the Greek population. The aim of the present study was to establish reference values for IgE in Greece.

There is no doubt that many factors limit the practical use of these results when applied to the general population. These factors include the technique employed, the expression of the results, and the difficulties in the methodology employed. In the present

study we used the PRIST method (7) since it is unanimously considered the most sensitive for the determination of very low levels of IgE (12). The results are expressed in iu/ml and because of the wide distribution of IgE levels, a logarithmic transformation was performed. The results of our study refer exclusively to healthy Greek adults of both sexes from practically every part of the country; according to the method employed, the sample is considered to be representative of the Greek population.

Male and female subjects included in the nonatopic group may not form an exclusively defined nonallergic population. This is because in studies like ours the skin tests employed include a rather limited number of allergens. Therefore, it is not improbable that some people with negative skin tests may show positive reactions when tested with a full battery of allergens.

At present, skin tests are still simple, practical, easy to perform, and reliable for detecting atopic individuals (23, 25). It is already known that IgE levels are characteristically increased in subjects with positive skin tests (28). This observation correlates well with our results where atopic males and females had higher IgE levels than nonatopic subjects. What is obvious from our results is that IgE levels showed a declining tendency depending on age, but the correlation was statistically nonsignificant in both nonatopic men and women. Opinions diverge on this subject. Barbee et al. (3) reported that IgE levels increased in an age-dependent manner in both men and women, while Delespesse et al. (9) reported lower IgE levels in adults aged over 70 years than in individuals under 40 years. On the other hand, Holford-Strevens et al. (14) studied nonatopic men and women and found no correlation between IgE levels and age, while Merrett et al. (22), in a general population sample, reported no differences between subjects aged 70 years and those aged 20 to 44 years. It is also known that IgE levels increase in childhood, reaching their peak during adolescence (3, 4, 19, 20). As a consequence, IgE levels differed when these age groups were included in the aforementioned studies. In our study IgE levels were higher in men than in women, but the difference was only statistically significant in nonatopic subjects. There is also a debate regarding the influence of gender on IgE levels. Many authors have observed that men have higher IgE levels than women (3, 5, 9, 27); others have not observed this (14, 26, 29). A possible explanation derives from the fact that IgE levels are smoking-dependent (2, 6, 30). Holford-Strevens et al. (14) studied nonatopic subjects and reported that IgE levels were higher in men than in women when smokers were excluded. When this group was excluded from the study, the difference observed was eliminated. A possible explanation of these observations is that men are heavier smokers than women or that the influence of smoking is apparent exclusively in men.

Table 4. Comparison of IgE levels of nonatopic men (M) and women (W) of different origin

	USA[8]			Canada[15]			Greece		
Age (yr)		*n*	IgE	Age (yr)	*n*	IgE	Age (yr)	*n*	IgE
6–14	M	130	42.7	–	–	–	–	–	–
	W	73	43.3	–	–	–	–	–	–
15–24	M	227	3.6	20–24	44	12.8	20–24	80	36.2
	W	121	18.6	20–24	32	21.6	20–24	66	34.0
25–34	M	201	16.8	25–34	75	14.9	25–29	98	50.1
	W	89	16.6	25–34	95	12.2	25–29	50	32.0
35–44	M	107	21.7	35–44	73	14.9	30–34	85	38.7
	W	67	19.3	35–44	67	9.9	30–34	55	26.5
45–54	M	141	19.2	45–54	53	14.8	35–39	76	39.0
	W	97	13.3	45–54	70	12.3	35–39	26	22.9
55–64	M	156	21.3	55–64	89	15.4	40–44	71	37.7
	W	172	11.7	55–64	95	11.4	40–44	30	26.7
65–74	M	194	21.2	–	–	–	45–49	70	30.4
	W	199	11.5	–	–	–	45–49	13	25.0
>75	M	85	18.4	–	–	–	>50	56	31.9
	W	87	9.2	–	–	–	>50	36	26.3
Total	M	1241	22.9	Total M	334	14.7	Total M	536	38.0
	W	905	14.7	W	359	12.1	W	276	29.3

The results of our study regarding IgE levels in nonatopic men and women as compared to similar findings from North America (3, 14) are presented in Table 4. In these studies a similar methodology was employed, and the IgE estimation was performed with the same assay (PRIST). Greek men and women showed slightly higher serum total IgE levels when compared to subjects from the USA (3) and Canada (14). The influence of genetic or environmental factors (e.g. parasitic infections etc.) is not known as yet.

In conclusion: 1) atopic men and women experienced higher IgE levels, as compared to nonatopic subjects, 2) IgE is not age-dependent in nonatopic men and women, 3) serum IgE levels were higher in nonatopic men than women, and 4) the Greek nonatopic population had higher IgE levels, as compared to a similar population from other Western countries.

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